9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1.2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido [1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo [9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7), 3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7), 3,5-triene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$] pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$. $0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2.10}$. $0^{4.8}$]pentadeca-2(10),3,6,8-tetraene;
10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene-5-carbonitrile;
1-[11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
1-[11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;
4-fluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene-5-carbonitrile;
5-fluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene-4-carbonitrile;
6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2.10}$. $0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$] hexadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$. $0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2.10}$. $0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2.10}$. $0^{4.8}$]hexadeca-2(10),3,6,8-tetraene;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene; and
11-aza-tricyclo[7,3,1.$0^{2.7}$]trideca-2(7),3,5-trien-5-ol and the pharmaceutically acceptable salts and optical isomers of the foregoing compounds.

[0014] In another more specific embodiment, the anti-depressant is selected from amitriptyline, imipramine, sertraline, paroxetine, fluoxetine, bupropion, nefazodone, phenelzine, tranylcypromine, moclobemide, venlafaxine, and the pharmaceutically acceptable salts and optical isomers isomers. A preferred anti- depressant is buproprion hydrochloride or one of its optical isomers.

[0015] The anxiolytic agent can be a benzodiazepine or a non-benzodiazepine and are selected from diazepam, alprazolam, chlordiazepoxide, buspirone, hydroxyzine or doxepin or a pharmaceutically acceptable salt or their optical isomers thereof.

[0016] A preferable anxiolytic agent is doxepin. The nicotine receptor partial agonist and the anti-depressant or anxiolytic agent can be administered substantially simultaneously.

[0017] The method also comprises administering to a mammal a nicotine receptor partial agonist or a pharmaceutically acceptable salt in amounts that render the composition effective in the treatment of tobacco or nicotine addiction, nicotine withdrawal symptoms, alcohol dependence or cocaine or other substance addiction. The nicotine partial receptor agonist is selected from

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido [1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido [1,2-a][1,5]diazocin-8-one;
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1.5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1.5-methano-pyrido[1,2-a][1.5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4,5.6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
4,5-difluoro-10-aza-tricyclo[6.3,1.$0^{2.7}$]dodeca-2(7),3,5-triene;
5-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-methyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,6,8-tetraene;
4-chloro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-ol;
7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2,4(8),6,9-tetraene;
4,5-dichloro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene-5-carbonitrile;
1-[11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
1-[11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;
4-fluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene-5-carbonitrile;
5-fluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene-4-carbonitrile;
6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
5,6-dimethyl-5,7,14-triazatetracydo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,6,8-tetraene;
5-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,6,8-tetraene;
6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
5,8,15-triazatetracyclo[11.3.1.$0^{2.11}$.$0^{4.9}$]heptade-

ca-2(11),3,5,7,9-pentaene;
7-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6,7-dimethyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
7-oxa-5,14-diazatetracydo[10,3,1,$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
7-methyl-5-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
4,5-difluoro-11-azatricyclo[7.3.1,$0^{2,7}$]trideca-2(7),3,5-triene;
4-chloro-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-chloro-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
4-(1-ethynyl)-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-(1-ethynyl)-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-6-ol;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol;
4-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene and

their pharmaceutically acceptable salts and their optical isomers.

[0018] A preferable nicotine receptor partial agonist is selected from

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1 ,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl-1-ethanone;
11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;
4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;
5-fluoro-1-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;
6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.

$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-methoxy-1-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol and

their pharmaceutically acceptable salts and their optical isomers.

[0019] The term "treating" as used herein, refers to reversing, alleviating, inhibiting or slowing the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0020] The chemist of ordinary skill will recognize that certain compounds of this invention will contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereoisomers and configurational isomers. All such isomers and mixture thereof are included in this invention. Hydrates of the compounds of this invention are also included.

[0021] The chemist of ordinary skill will recognize that certain combinations of heteroatom-containing substituent listed in this invention define compounds which will be less stable under physiological conditions (e.g., those containing acetal or animal linkages). According, such compounds are less preferred.

Detailed Description of the Invention

[0022] In combination with the NRPA, the invention includes an anti-depressant agent or a pharmaceutically acceptable salt of compounds such as a tricyclic antidepressant (e.g. amitryptyline, imipramine), a serotonin reuptake inhibitor anti-depressant (SRI) (e.g. sertraline, paroxetine, or fluoxetine), an atypical antidepressant (bupropion, nefazodone) or a monoamine oxidase inhibitor (e.g., phenelzine, tranylcypromine), and compounds in U.S. Patent No. 4,536,518 and may be used in this invention.

[0023] In combination with the NRPA, the invention may include an anxiolytic agent or pharmaceutically acceptable salt of compounds such as a benzodiazepine (e.g. diazepam, alprazolam, chlordiazepoxide) or non-benzodiazepine anxiolytic (e.g. buspirone, hydroxyzine, doxepin).

[0024] The particular NRPA compounds listed above, which can be employed in the method and pharm, compositions of this invention, can be made by processes known in the chemical arts, for example by the methods described in WO 9818798 A1, WO 9935131-A1 and United States Provisional Patent Application No. 60/083,556 filed April 29, 1998. Some of the preparation methods useful for making the compounds of this invention may require protection of remote functionality (i.e., primary amine, secondary amine, carboxyl). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art, and is described in examples carefully described in the above cited applications. The starting materials and reagents for the NRPA compounds employed in this invention are also readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. Some of the compounds used herein are related to, or are derived from compounds found in nature and accordingly many such compounds are commercially available or are reported in the literature or are easily prepared from other commonly available substances by methods which are reported in the literature.

[0025] Some of the NRPA compounds employed in this invention are ionizable at physiological conditions. Thus, for example some of the compounds of this invention are acidic and they form a salt with a pharmaceutically acceptable cation. All such salts are within the scope of this invention and they can be prepared by conventional methods. For example, they can be prepared simply by contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate.

[0026] In addition, some of the NRPA compounds employed in this invention are basic, and they form a salt with a pharmaceutically acceptable anion. All such salts are within the scope of this invention and they can be prepared by conventional methods. For example, they can be prepared simply by contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate.

[0027] In addition, when the NRPA compounds employed in this invention form hydrates or solvates they are also within the scope of the invention.

[0028] Some of the compounds of this invention are chiral, and as such are subject to preparation via chiral synthetic routes, or separable by conventional resolution or chromatographic means. All optical forms of the compounds of this invention are within the scope of the invention.

[0029] The utility of the NRPA compounds employed in the present invention as medicinal agents in the treatment of nicotine dependence (such as tobacco depend-

ence or addiction) in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in conventional assays and, in particular the assays described below. These include neuronal nicotinic receptor binding, dopamine turnover, and animal models of depression (mouse behavioral despair) and anxiety (Vogel anti-conflict). Such assays also provide a means whereby the activities of the compounds of this invention can be compared between themselves and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

Biological Assays

Procedures

[0030] Receptor binding assay: The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites is determined by the following procedure which is a modification of the methods of Lippiello, P. M. and Fernandes, K. G. (in The Binding of L-[^{3}H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes, Molecular Pharm., 29, 448-54, (1986)) and Anderson, D. J. and Americ, S. P. (in Nicotinic Receptor Binding of ^{3}H-Cystisine, ^{3}H-Nicotine and ^{3}H-Methylcarmbamylcholine In Rat Brain, European J. Pharm., 253, 261-67 (1994)). Male Sprague-Dawley rats (200-300 g) from Charles River were housed in groups in hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.-7 p.m. light period). They received standard Purina Rat Chow and water *ad libitum*. The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (Molec Pharmacol, 29, 448-454, (1986) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0° in 10 volumes of buffer (w/v) using a Brinkmann Polytron™, setting 6, for 30 seconds. The buffer consisted of 50 mM Tris HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10 minutes; 50,000 x g; 0° to 4°C). The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000 x g; 0 to 4°C. After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0g/100mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$ and has a pH of 7.4 at room temperature.

[0031] Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50µL of vehicle, blank, or test compound solution, respectively. To each tube was added 200µL of [^{3}H]-nicotine in assay buffer followed by 750µL of the membrane suspension. The final concentration of nicotine in each tube was 0.9 nM. The final concentration of cytisine in the blank was 1µM. The vehicle consisted of deionized water containing 30µL of 1 N acetic acid per 50 mL of water. The test compounds and cytisine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0° to 4° C in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B™ glass fiber filters using a Brandel™ multi-manifold tissue harvester. Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 m each). The filters were then placed in counting vials and mixed vigorously with 20 ml of Ready Safe™ (Beckman) before quantification of radioactivity. Samples were counted in a LKB Wallach Rackbeta™ liquid scintillation counter at 40-50% efficiency. All determinations were in triplicate.

[0032] Calculations: Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytisine (B), i.e.,

$$\text{Specific binding} = (C) = (A) - (B).$$

[0033] Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e., (E) = (D) - (B).

$$\%\ \text{Inhibition} = (1-((E)/(C)) \text{ times } 100.$$

[0034] The compounds of the invention that were tested in the above assay exhibited IC_{50} values of less than 10µM.

[0035] Dopamine Turnover: Rats were injected s.c. or p.o. (gavage) and then decapitated either 1 or 2 hours later. Nucleus accumbens was rapidly dissected (2 mm slices, 4°C, in 0.32 M sucrose), placed in 0.1 N perchloric acid, and then homogenized. After centrifugation 10uL of the supernatant was assayed by HPLC-ECD. Turnover/ utilization of dopamine (DA) was calculated as the ratio of tissue concentrations of metabolites ([DOPAC]+[HVA]) to DA and expressed as percent of control.

[0036] Mouse behavioral despair test: The ability of various agents to delay the onset of immobility was assayed in a behavioral despair test (Porsolt RD; Bertin A; Jalfre MI; 1979; Arch Int Pharmacodyn Ther; 229 (2) p327-36). Male CD-1 mice from Charles River, weighing 14-16 g on arrival and 25-35 g at the time of testing serve

as subjects. Mice are housed 10/cage under standard laboratory conditions on a L:D/7a.m.:7p.m. lighting cycle of at least 7 days prior to experimentation. Food and water are available ad libitum until the time of testing. All compounds are administered in a volume of 10 ml/kg. Agent vehicles will depend on compound solubiltiy, but testing will typically be done using saline or distilled water as the injection vehicle.

[0037] Subjects are administered test compound (sc, ip. or po) at a predetermined pretreatment time. At the test time, groups of ten mice are placed individually in 1000 ml beakers filled with water to the 700 ml mark at 22-23°C. A five minute test is started after the last subject is placed in the beakers with ratings taken every thirty seconds. Ratings were either 1 for immobile swim or 0 for mobile swim. The ten ratings were then totaled for each subject and the data was anaylzyed with Kruskall-Wallis and Mann-Whitney U tests.

[0038] Vogel Anticonflict assay: The ability of various agents to increase punished responding was evaluated using a modification of the procedure described by Vogel, Beer and Clody (Psychopharmacologia 21(1); 1971). The test chambers consisted of clear plexiglass boxes (25 cm L x 22 cm W x 22 cm H) equipped with a stainless steel drinking tube and a floor of stainless steel bars, housed in sound-attenuating wooden cabinets. Training and testing were conducted between 900 and 1600 h. After 48 hours of water deprivation, rats (N=8/group) were placed into the test chambers for a training period, in which they were allowed to explore the chamber and drink water freely for up to three minutes. Animals that did not locate the drinking spout within 10 minutes were excluded from agent testing. Animals were then administered vehicle or agent (i.p.) and were placed back into the chambers for conflict testing after a 15 min agent pretreatment period. After every 20 unpunished licks, subsequent licking resulted in the presentation of a 0.5 mA current (0.5 sec duration) applied between the drinking tube and the grid floor. The number of shocks taken in a ten minute test period was recorded by computer and data were analyzed with ANOVA followed by Dunnett's t-tests for multiple comparisons to a single control. Animals that did not begin to drink within five minutes after placement in the chamber were eliminated from the experiment and behavioral disruption due to agent treatment was assumed to have occurred.

[0039] Administration of the compositions of this invention can be via any method which delivers a compound of this invention systemically and/or locally. These methods include oral routes and transdermal routes, etc. Generally, the compounds of this invention are administered orally, but parenteral administration may be utilized (e.g., intravenous, intramuscular, subcutaneous or intramedullary). The two different compounds of this invention can be co-administered simultaneously or sequentially in any order, or a single pharmaceutical composition comprising a NRPA as described above and an anti-depressant or anxiolytic as described above in a pharmaceutically acceptable carrier can be administered.

[0040] The amount and timing of compounds administered will, of course, be based on the judgement of the prescribing physician. Thus, because of patient to patient variability, the dosages given below are a guideline and the physician may titrate doses of the agent to achieve the activity that the physician considers appropriate for the individual patient. In considering the degree of activity desired, the physician must balance a variety of factors such as cognitive function, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular). The following paragraphs provide preferred dosage ranges for the various components of this invention (based on average human weight of 70 kg).

[0041] In general, an effective dosage for the NRPA in the range of 0.01 to 200 mg/kg/day, preferably 0.05 to 10.0 mg/kg/day.

[0042] In particular, an effective dosage for sertraline, when used in the combination compositions and methods of this invention, is in the range of 0.01 to 1.0 mg/kg/day.

[0043] In particular, an effective dosage for paroxetine, when used in the combination compositions and methods of this invention, is in the range of 0.1 to 7.0 mg/kg/day.

[0044] In particular, an effective dosage for fluoxetine, when used in the combination compositions and methods of this invention, is in the range of 0.1 to 1.1 mg/kg/day.

[0045] In particular, an effective dosage for nefazodone, when used in the combination compositions and methods of this invention, is in the range of 1.4 to 8.6 mg/kg/day.

[0046] In particular, an effective dosage for amitryptyline, when used in the combination i compositions and methods of this invention, is in the range of 0.1 to 3.0 mg/kg/day.

[0047] In particular, an effective dosage for imipramine, when used in the combination compositions and methods of this invention, is in the range of 0.1 to 1.5 mg/kg/day.

[0048] In particular, an effective dosage for bupropion, when used in the combination compositions and methods of this invention, is in the range of 0.1 to 10.0 mg/kg/day.

[0049] In particular, an effective dosage for phenelzine, when used in the combination compositions and methods of this invention, is in the range of 1.0 to 4.3mg/kg/day

[0050] In particular, an effective dosage for tranylcypromine, when used in the combination compositions and methods of this invention, is in the range of 0.1 to 0.9 mg/kg/day

[0051] In particular, an effective dosage for moclobemide, when used in the combination compositions

and methods of this invention, is in the range of 1.0 to 15 mg/kg/day

[0052] In particular, an effective dosage for venlafaxine, when used in the combination compositions and methods of this invention, is in the range of 0.1 to 5.0 mg/kg/day

[0053] In particular, an effective dosage for diazepam, when used in the combination compositions and methods of this invention, is in the range of 0.02 to 2 mg/kg/day.

[0054] In particular, an effective dosage for alprazolam, when used in the combination compositions and methods of this invention, is in the range of 0.003 to 0.2 mg/kg/day.

[0055] In particular, an effective dosage for chlordiazepoxide, when used in the combination compositions and methods of this invention, is in the range of 0.07 to 1.4 mg/kg/day.

[0056] In particular, an effective dosage for bupropion, when used in the combination compositions and methods of this invention, is in the range of 0.1 to 0.9 mg/kg/day.

[0057] In particular, an effective dosage for hydroxyzine, when used in the combination compositions and methods of this invention, is in the range of 0.14 to 6 mg/kg/day.

[0058] In particular, an effective dosage for doxepin, when used in the combination compositions and methods of this invention, is in the range of 0.3 to 4.3 mg/kg/day.

[0059] The compositions of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable vehicle or diluent. Thus, the compounds of this invention can be administered individually or together in any conventional oral, parenteral or transdermal dosage form.

[0060] For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipient such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[0061] For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

[0062] For purposes of transdermal (e.g.,topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

[0063] Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

[0064] Pharmaceutical compositions according to the invention may contain 0.1%-95% of the compound(s) of this invention, preferably 1%-70%. In any event, the composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the dependence of the subject being treated.

Claims

1. A pharmaceutical composition for treating nicotine dependence or addiction, tobacco dependence or addiction, reducing nicotine withdrawal symptoms or aiding in the cessation or lessening of tobacco use or substance abuse, comprising a therapeutically effective combination of a nicotine receptor partial agonist and an anti-depressant or anxiolytic agent, and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to Claim 1, wherein said anti-depressant is selected from tricyclic anti-depressant, a serotonin reuptake inhibitor anti-depressant (SRI), an atypical anti-depressant or a monoamine oxidase inhibitor, their pharmaceutically active salts and their optical isomers.

3. The pharmaceutical composition according to Claim 2, wherein said anti-depressant is selected from amitryptyline, imipramine, sertraline, paroxetine, fluoxetine, buproprion nefazodone, tranylcypromine, moclobemide, venlafaxine, or phenelzine,

their pharmaceutically active salts and their optical isomers.

4. The pharmaceutical composition according to Claim 1 wherein said anxiolytic agent is selected from a benzodiazepine or a non-benzodiazepine anxiolytic, their pharmaceutically active salts and their optical isomers.

5. The pharmaceutical composition according to Claim 4, wherein the anxiolytic agents are selected from diazepam, alprazolam, hydroxyzine or doxepin, their pharmaceutically active salts and their optical isomers.

6. The pharmaceutically composition according to Claim 1, wherein said nicotine receptor partial agonist is selected from

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-oxo-6,13-diazatetracydo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$] pentadeca-2(10),3,8-triene;
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$] pentadeca-2(10),3,8-triene;
4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene;
5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-methyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene;
7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,13-triazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10), 3,5,8-tetraene;
6-methyl-7-phenyl-5,7,13-triazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10), 3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo [10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$] pentadeca-2(10),3,6,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10), 3,6,8-tetraene;
4-chloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2 (7),3,5-triene;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-trien-4-yl)-1-ethanone;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol;
7-methyl-5-oxa-6,13-diazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8), 6,9-tetraene;
4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7), 3,5-triene-5-carbonitrile;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;
4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7), 3,5-triene-5-carbonitrile;
5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7), 3,5-triene-4-carbonitrile;
6-methyl-7-thia-5,14-diazatetracyclo [10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10), 3,5,8-tetraene;
6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$. $0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,14-triazatetracyclo [10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10), 3,5,8-tetraene;
5,7,14-triazatetracydo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,6-dimethyl-5,7,14-triazatetracyclo [10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10), 3,6,8-tetraene;
5-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$. $0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo [10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10), 3,5,8-tetraene;
5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
7-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$. $0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$. $0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6,7-dimethyl-5,8,15-triazatetracyclo [11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11), 3,5,7,9-pentaene;
7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$] hexadeca-2(10),3,5,8-tetraene;
6-methyl-7-oxa-5,14-diazatetracyclo [10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10), 3,5,8-tetraene;
5-methyl-7-oxa-6,14-diazatetracyclo [10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10), 3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo [10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10), 3,6,8-tetraene;
7-methyl-5-oxa-6,14-diazatetracyclo [10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10), 3,6,8-tetraene;
4,5-difluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2 (7),3,5-triene;
4-chloro-5-fluoro-11-azatricyclo[7.3.1,$0^{2,7}$]trideca-2(7),3,5-triene;
5-chloro-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
4-(1-ethynyl)-5-fluoro-11-azatricyclo [7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-(1-ethynyl)-4-fluoro-11-azatricyclo [7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2 (7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-6-ol;
6-fluoro-11-aza-tricyclo[7.3,1.$0^{2,7}$]trideca-2(7), 3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol;
4-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7), 3,5-triene;
5-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7), 3,5-triene;
5-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7), 3,5-triene;
6-hydroxy-5-methoxy-11-aza-tricyclo [7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and

their pharmaceutically acceptable salts and their optical isomers.

7. A method of treating a mammal which presents with tobacco or nicotine addiction, nicotine withdrawal symptoms, alcohol dependence or cocaine or other substance addiction, comprising administering to said mammal:

a. a nicotine receptor partial agonist or a pharmaceutically acceptable salt thereof; and
b. an anti-depressant or anxiolytic agent or a pharmaceutically acceptable salt thereof, wherein the nicotine receptor partial agonist and the anti-depressant or anxiolytic agent are present in amounts that render the composition effective in the treatment of tobacco or nicotine addiction, nicotine withdrawals symptoms, al-

cohol dependence or cocaine or other substance addiction.

8. The method of daim 7, wherein the anti-depressant is selected form tricyclic anti-depressants, serotonin reuptake inhibitor anti-depressants, atypical anti-depressants, or monoamine oxidase inhibitors, and the pharmaceutically active salts and optical isomers thereof.

9. The method according to claim 7 wherein the anxiolytic agent is selected from benzodiazepine and non-benzodiazepine anxiolytic agents and their pharmaceutically acceptable salts and optical isomers.

10. The method according to claim 8 wherein the anti-depressant is selected from amitriptyline, imipramine, sertraline, paroxetine, fluoxetine, bupropion, nefazodone, moclobemide, venlafaxine, phenelzine, tranylcypromine, and the pharmaceutically acceptable salts and optical isomers thereof.

11. The method according to claim 9 wherein the anxiolytic agent is selected from diazepam, chlordiazepoxide, buspirone, hydroxyzine or doxepin or a pharmaceutically acceptable salt or an optical isomer thereof.

12. The method according to claim 8, wherein the nicotine partial agonist is selected from

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4.5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-oxo-6,13-diazatetracyclo [9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
5-oxo-6,13-diazatetraycyclo[9.3.1.$0^{2.10}$.$0^{4.8}$] pentadeca-2(10),3,8-triene;
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$] pentadeca-2(10),3,8-triene;
4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
5-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2 (7),3,5-triene-4-carbonitrile;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$] dodeca-2(7),3,5-triene;
5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2 (7),3,5-triene-4-carbonitrile;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo [9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7), 3,5-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2 (7),3,5-triene;
4-methyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2 (7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7), 3,5-triene;
7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$. $0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$. $0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,13-triazatetracyclo [9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),

3,5,8-tetraene;
6-methyl-7-phenyl-5,7,13-triazatetracydo [9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10), 3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo [10.3,1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracydo[9.3.1.$0^{2.10}$.$0^{4.8}$] pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo [9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10), 3,6,8-tetraene;
4-chloro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7), 3,5-trien-4-yl)-1-ethanone;
10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-ol;
7-methyl-5-oxa-6,13-diazatetracyclo [9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2,4(8), 6,9-tetraene;
4,5-dichloro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene-5-carbonitrile;
1-[11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
1-[11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;
4-fluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene-5-carbonitrile;
5-fluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene-4-carbonitrile;
6-methyl-7-thia-5,14-diazatetracyclo [10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10), 3,5,8-tetraene;
6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,14-triazatetracyclo [10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10), 3,5,8-tetraene;
5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
5,6-dimethyl-5,7,14-triazatetracyclo [10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10), 3,6,8-tetraene;
5-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,6,8-tetraene;
6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo [10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10), 3,5,8-tetraene;
5,8,15-triazatetracyclo[11.3.1.$0^{2.11}$.$0^{4.9}$]hepta-deca-2(11),3,5,7,9-pentaene;
7-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2.11}$.$0^{4.9}$]heptadeca-2(11),3,5,7,9-pentaene;
6-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2.11}$.$0^{4.9}$]heptadeca-2(11),3,5,7,9-pentaene;
6,7-dimethyl-5,8,15-triazatetracyclo [11.3.1.$0^{2.11}$.$0^{4.9}$]heptadeca-2(11), 3,5,7,9-pentaene;
7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$] hexadeca-2(10),3,5,8-tetraene;
6-methyl-7-oxa-5,14-diazatetracyclo [10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10), 3,5,8-tetraene;
5-methyl-7-oxa-6,14-diazatetracyclo [10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10), 3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracydo [10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10), 3,6,8-tetraene;
7-methyl-5-oxa-6,14-diazatetracyclo [10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10), 3,6,8-tetraene;
4,5-difluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
4-chloro-5-fluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
5-chloro-4-fluoro-11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
4-(1-ethynyl)-5-fluoro-11-azatricyclo [7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
5-(1-ethynyl)-4-fluoro-11-azatricyclo [7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-6-ol;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-5-ol;
4-nitro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene;
5-nitro-1-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene;
5-fluoro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7), 3,5-triene;
6-hydroxy-5-methoxy-11-aza-tricyclo [7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene

and a pharmaceutically acceptable salt and an optical isomer thereof.

13. The method according to claim 7, wherein the nicotine receptor partial agonist and the anti-depres-

sant or anxiolytic agent are administered substantially simultaneously.

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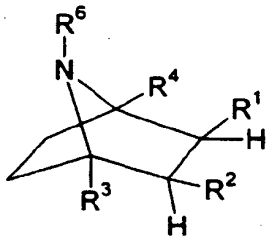
(54) 7-aza-bicyclo[2.2.1]-heptane derivatives, their preparation and use according to their affinity for neuronal nicotinic acetylchloline receptors

(57) Compounds of the formula



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and their pharmaceutically acceptable salts, wherein R^1, R^2, R^3 and R^4 are defined as in the specification, intermediates in the synthesis of such compounds, pharmaceutical compositions containing such compounds and methods of using such compounds in the treatment of neurological and psychological disorders are claimed.

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Description

Background of the Invention

[0001] This invention relates to 7-hetero-bicyclo[2.2.1]-heptanes, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

[0002] The compounds of this invention may also be used in combination with an antidepressant such as a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's Chorea or traumatic brain injury (TBI); in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD, stroke, Huntington's Chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD stroke, Huntington's Chorea and TBI: or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal antiinflammatory agents and estrogen-like therapy.

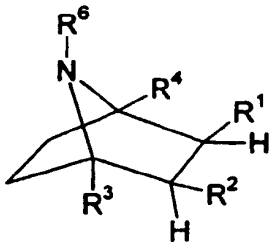
[0003] Other compounds that bind to neuronal nicotinic receptor sites are referred to in United States Patent Application 08/963,852, which was filed on November 4, 1997.

[0004] In Devop of the Future, 1997, 22 (11): 1210-1220, Donglu Bai et al., reviews methods of synthesizing epibatidine and the pharmacological properties of epibatidine.

[0005] Epibatidine derivatives and their various pharmacological activities are referred to, inter alia, in the following references: United States patent application 845,042, filed March 3, 1992; Japanese patent application JP 6312989A2, published November 8, 1994; World patent application WO 95/03306, published February 2, 1995; Japanese patent application JP 7010878A2, published January 13, 1995; Japanese patent application 7033771A2, published February 3, 1995. World patent application 95/07078A1, published March 16, 1995; United States patent US 5,346,906, issued September 13, 1994; European patent application EP 657455A1, published June 14, 1994; Japanese patent application JP 7061940A2, published March 7, 1995; European patent application EP 664293A1, published July 26, 1995; World patent application WO 94/22868A1, published October 13, 1994; and World patent application WO 96/06093, published February 29, 1996.

Summary of the Invention

[0006] This invention relates to aryl fused azapolycyclic compounds of the formula



I

wherein

R^1, R^2, R^3 and R^4 are selected, independently from hydrogen, $-CO_2R^5$, aryl and heteroaryl, wherein said aryl is

selected from phenyl and naphthyl and said heteroaryl is selected from pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, 1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolinyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl oxazolyl, isoxazoyl, thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl, pyridinyl, and pyrimidinyl, and wherein said phenyl and said heteroaryl may optionally be substituted with from one to three substitutuents, and are preferably substituted with one or two substutituents, independently selected form (C_1-C_6) alkyl optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, halo (i.e., chloro, fluoro, bromo or iodo), phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C_1-C_6)alkoxy optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, (C_1-C_6)alkylamino and [(C_1-C_6) alkyl]$_2$amino;

R^5 is (C_1-C_6) alkyl, aryl, heteroaryl, (C_1-C_4)alkylene-aryl and (C_1-C_4)alkylene-heteroaryl, wherein said aryl and heteroaryl are defined as above, and wherein said (C_1-C_6)alkyl may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_4)alkoxy-(C_1-C_4)alkyl, amino, (C_1-C_6)alkylamino, and [(C_1-C_6)alkyl]$_2$amino; and

R^6 is hydrogen or (C_1-C_6)alkyl;

with the proviso that: (a) at least one of R^1, R^2, R^3, and R^4 must be aryl or heteraryl; (b) when neither R^1 nor R^2 is hydrogen, R^1 and R^2 are in the "exo" configuration; (c) R^1 and R^2 can not both be $-CO_2R^5$; (d) if either R^3 or R^4 is $-CO_2R^5$ and R^5 is an alkyl or alkoxyalkyl group, then one of R^1 and R^2 must be aryl or heteroaryl; and (e) if either R^1 or R^2 is $-CO_2R^5$ and R^5 is an alkyl or alkoxyalkyl group, then one of R^3 and R^4 must be aryl or heteroaryl;

and the pharmaceutically acceptable salts of such compounds.

[0007] Preferred compounds of this invention include compounds of the formula I, and their pharmaceutically acceptable salts, wherein one of R^1 and R^2 is optionally substituted phenyl and the other is hydrogen, and wherein R^3 and R^4 are hydrogen.

[0008] More preferred compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein one of R^1 and R^2 is phenyl substituted with fluoro or nitro and the other is hydrogen, and wherein R^3 and R^4 are hydrogen.

[0009] More specific preferred embodiments of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^3 and R^4 are hydrogen and one R^1 and R^2 is hydrogen and the other is: (a) 3-fluorophenyl; (b) 4-nitrophenyl; or 3-fluoro-4-nitrophenyl.

[0010] Other embodiments of this invention relate to the following compounds of the formula I and their pharmaceutically acceptable salts:

2β-(3,4-difluorophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3,5-dichlorobenzene)-7-aza-bicyclo[2.2.1]heptane;
2β-(4-nitrophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-thiophene)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-fluoro-4-chlorophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-flourophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-hydroxyphenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-acetophenone)-7-aza-bicyclo[2.2. 1]heptane;
2β-(4-trifluoromethylphenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-fluoro-4-methylphenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-chlorophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(n-benzyl-5-pyridonyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(n-methyl-5-pyridonyl)- 7-aza-bicyclo[2.2.1]heptane;
2β-(3-fluoro-5-nitrophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(4-aminophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-fluoro-4-trifluoromethyl-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(4-chlorophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3,4-methylenedioxyphenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(2-chloro-6-methyl-5-pyridinyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(4-cyanophenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-fluoro-4-nitro-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(4-amido-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-fluoro-4-amino-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2β-(4-sulfonamido-phenyl)-7-aza-bicyclo[2.2.1]heptane;

2β-(3-methyl-5-isoxzazole)-7-aza-bicyclo[2.2.1]heptane;
2β-(3-methyl-5-isoxzazole)-7-aza-bicyclo[2.2.1]heptane. N-methyl;
2β-(3-methyl-5-isoxzazole)-7-aza-bicyclo[2.2.1]heptane. N-acetyl;
2b-(3,4-difluorophenyl)-7-azabicyclo[2.2.1]heptane;
4-(7-aza-bicyclo[2.2.1]hept-2-yl)-benzamidine;
2-(4-methanesulfonyl-phenyl)-7-aza-bicyclo[2.2.1]heptane;
4-(7-aza-bicyclo[2.2.1]hept-2-yl)-phenol;
2-(4-methylsulfanyl-phenyl)-7-aza-bicyclo[2.2.1]heptane;
4-(7-aza-bicyclo[2.2.1]hept-2-yl)-benzoic acid methyl ester;
4-(7-aza-bicyclo[2.2.1]hept-2-yl)-benzoic acid;
2-(3-fluoro-4-tetrazol-1-yl-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-(4-nitro-3-trifluoromethyl-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-[3-fluoro-4-(5-trifluoromethyl-tetrazol-1-yl)-phenyl]-7-aza-bicyclo[2.2.1]heptane;
2-(3-chloro-4-nitro-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-(4-tetrazol-1-yl-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-(6-methoxy-pyridin-2-yl)-7-aza-bicyclo[2.2.1]heptane;
2-(4-methanesulfinyl-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-(4-bromo-3-fluoro-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-(4-cyano-3-fluoro-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-(3,4,5-trifluoro-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-(3,4,5-trimethoxy-phenyl)-7-aza-bicyclo[2.2.1]heptane;
2-(5-nitro-furan-2-yl)-7-aza-bicyclo[2.2.1]heptane;
5-(7-aza-bicyclo[2.2.1]hept-2-yl)-3-methyl-benzo[d]isoxazole;
6-(7-aza-bicyclo[2.2.1]hept-2-yl)-3-methyl-benzo[d]isoxazole;
6-(7-aza-bicyclo[2.2.1]hept-2-yl)-1,4-dihydro-quinoxaline-2,3-dione;
6-(7-aza-bicyclo[2.2.1]hept-2-yl)-quinoxaline; and
1-[4-(7-aza-bicyclo[2.2.1]hept-2-yl)-2-fluoro-phenyl]-ethanone.

[0011] Examples of specific compounds of the formula I are the following:

7-Azabicyclo[2.2.1]heptane, 2-(5-methyl-3-isoxazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-[5-(trifluoromethyl)-3-isoxazolyl]-;
7-Azabicyclo[2.2.1]heptane, 2-(5-chloro-3-isoxazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-methyl-3-isothiazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-[5-(trifluoromethyl)-3-isothiazolyl]-;
7-Azabicyclo[2.2.1]heptane, 2-(5-chloro-3-isothiazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(2-fluoro-1*H*-imidazol-4-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-[2-(trifluoromethyl)-1*H*-imidazol-4-yl]-;
7-Azabicyclo[2.2.1]heptane, 2-(2-chloro-1*H*-imidazol-4-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(2-methyl-1*H*-imidazol-4-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-[5-(trifluoromethyl)-1*H*-tetrazol-1-yl]-;
7-Azabicyclo[2.2.1]heptane, 2-(5-fluoro-1*H*-tetrazol-1-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-chloro-1*H*-tetrazol-1-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-[5-(trifluoromethyl)-1*H*-1,2,4-triazol-3-yl]-;
7-Azabicyclo[2.2.1]heptane, 2-(5-fluoro-1*H*-1,2,4-triazol-3-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-chloro-1*H*-1,2,4-triazol-3-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-methyl-1*H*-1,2,4-triazol-3-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(1*H*-tetrazol-5-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(1*H*-1,2,3-triazol-4-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(1*H*-pyrrol-2-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-;
7-Azabicyclo[2.2.1]heptane, 2-(5-fluoro-1,3,4-thiadiazol-2-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-chloro-1,3,4-thiadiazol-2-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-methyl-1,3,4-thiadiazol-2-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-;
7-Azabicyclo[2.2.1]heptane, 2-(5-fluoro-1,3,4-oxadiazol-2-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-chloro-1,3,4-oxadiazol-2-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-methyl-1,3,4-oxadiazol-2-yl)-;

7-Azabicyclo[2.2.1]heptane, 2-(5-methyl-1*H*-pyrazol-3-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-[5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-;
7-Azabicyclo[2.2.1]heptane, 2-(5-chloro-1*H*-pyrazol-3-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-(2-methyl-5-oxazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-[2-(trifluoromethyl)-5-oxazolyl]-;
7-Azabicyclo[2.2.1]heptane, 2-(2-chloro-5-oxazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(2-fluoro-5-oxazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(2-methyl-5-thiazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-[2-(trifluoromethyl)-5-thiazolyl]-;
7-Azabicyclo[2.2.1]heptane, 2-(2-chloro-5-thiazolyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(2-fluoro-5-thiazolyl)-;
Ethanone, 1-[4-(7-azabicyclo[2.2.1]hept-2-yl)-2-fluorophenyl]-2,2,2-trifluoro-;
7-Azabicyclo[2.2.1]heptane, 2-[2-(4-pyridinyl)ethenyl]-, (*E*)-;
7-Azabicyclo[2.2.1]heptane, 2-[2-(3-pyridinyl)ethenyl]-, (*E*)-;
7-Azabicyclo[2.2.1]heptane, 2-[2-(5-pyrimidinyl)ethenyl]-, (*E*)-;
7-Azabicyclo[2.2.1]heptane, 2-[2-(4-pyridazinyl)ethenyl]-, (*E*)-;
2(3*H*)-Benzoxazolone, 6-(7-azabicyclo[2.2.1]hept-2-yl)-4-fluoro-;
2(3*H*)-Benzothiazolone, 6-(7-azabicyclo[2.2.1]hept-2-yl)-4-fluoro-;
2*H*-Indol-2-one, 5-(7-azabicyclo[2.2.1]hept-2-yl)-7-fluoro-1,3-dihydro-;
2*H*-Benzimidazol-2-one,6-(7-azabicyclo[2.2.]hept-2-yl)-4-fluoro-1,3-dihydro-;
2*H*-Benzimidazol-2-one,6-(7-azabicyclo[2.2.1]hept-2-yl)-4-fluoro-1,3-dihydro-1-methyl-;
Ethanone, 1-[4-(7-azabicyclo[2.2.1]hept-2-yl)-2-fluorophenyl]-;
7-Azabicyclo[2.2.1]heptane, 2-(3-pyridinylethynyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(4-pyridinylethynyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(4-pyridazinylethynyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(5-pyrimidinylethynyl)-;
2(3*H*)-Benzoxazolone, 6-(7-azabicyclo[2.2.1]hept-2-yl)-;
2(3*H*)-Benzothiazolone, 6-(7-azabicyclo[2.2.1]hept-2-yl)-;
2*H*-Indol-2-one, 5-(7-azabicyclo[2.2.1]hept-2-yl)-1,3-dihydro-;
2*H*-Benzimidazol-2-one, 5-(7-azabicyclo[2.2.1]hept-2-yl)-1,3-dihydro-;
2*H*-Benzimidazol-2-one, 6-(7-azabicyclo[2.2.1]hept-2-yl)-1,3-dihydro-1-methyl-;
1-Propanone, 1-[4-(7-azabicyclo[2.2.1]hept-2-yl)-2-fluorophenyl]-3,3,3-trifluoro-;
7-Azabicyclo[2.2.1]heptane, 2-(4-azido-3-fluorophenyl)-;
Phenol, 5-(7-azabicyclo[2.2.1]hept-2-yl)-2-nitro-;
7-Azabicyclo[2.2.1]heptane, 2-(4-nitrocyclohexyl)-;
7-Azabicyclo[2.2.1]heptane, 2-(4-nitrobicyclo[2.2.2]oct-1-yl)-;
7-Azabicyclo[2.2.1]heptane, 2-[(6-chloro-3-pyridinyl)ethynyl]-;
7-Azabicyclo[2.2.1]heptane, 2-[2-(6-chloro-3-pyridinyl)ethenyl]-, (*E*)-;
1,5-Methano-8*H*-pyrido[1,2-a][1,5]diazocin-8-one, 9-(7-azabicyclo[2.2.1]hept-2-yl)-1,2,3,4,5,6-hexahydro-;
2(1*H*)-Pyridinone, 3-(7-azabicyclo[2.2.1]hept-2-yl)-1-methyl-: and
2(1*H*)-Pyridinone, 3-(7-azabicyclo[2.2.1]hept-2-yl)-.

[0012] This invention also relates to the pharmaceutically acceptable acid addition salts of the compounds of formula I. Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I are the salts of hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, malate, di-p-toluoyl tartaric acid, and mandelic acid.

[0013] Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

[0014] Unless otherwise indicated, the term "alkyl", as used herein, may be straight, branched or cyclic, and may include straight and cyclic moieties as well as branched and cyclic moieties.

[0015] Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

[0016] The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0017] The compounds of formula I may have optical centers and therefore may occur in different enantiomeric configurations. This invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula I, as well as racemic and other mixtures thereof.

[0018] The present invention also relates to all radiolabelled forms of the compounds of the formulae I. Preferred

radiolabelled compounds of formula I are those wherein the radiolabels are selected from as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

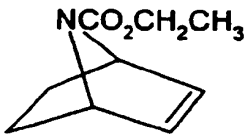
[0019] The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

[0020] The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

[0021] The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac anythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

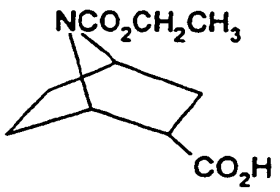
[0022] The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically accepable salt thereof, and a pharmaceutically acceptable carrier.

[0023] This invention also relates to a process for preparing a compound of the formula



XVI

comprising reacting a compound of the formula



XVII

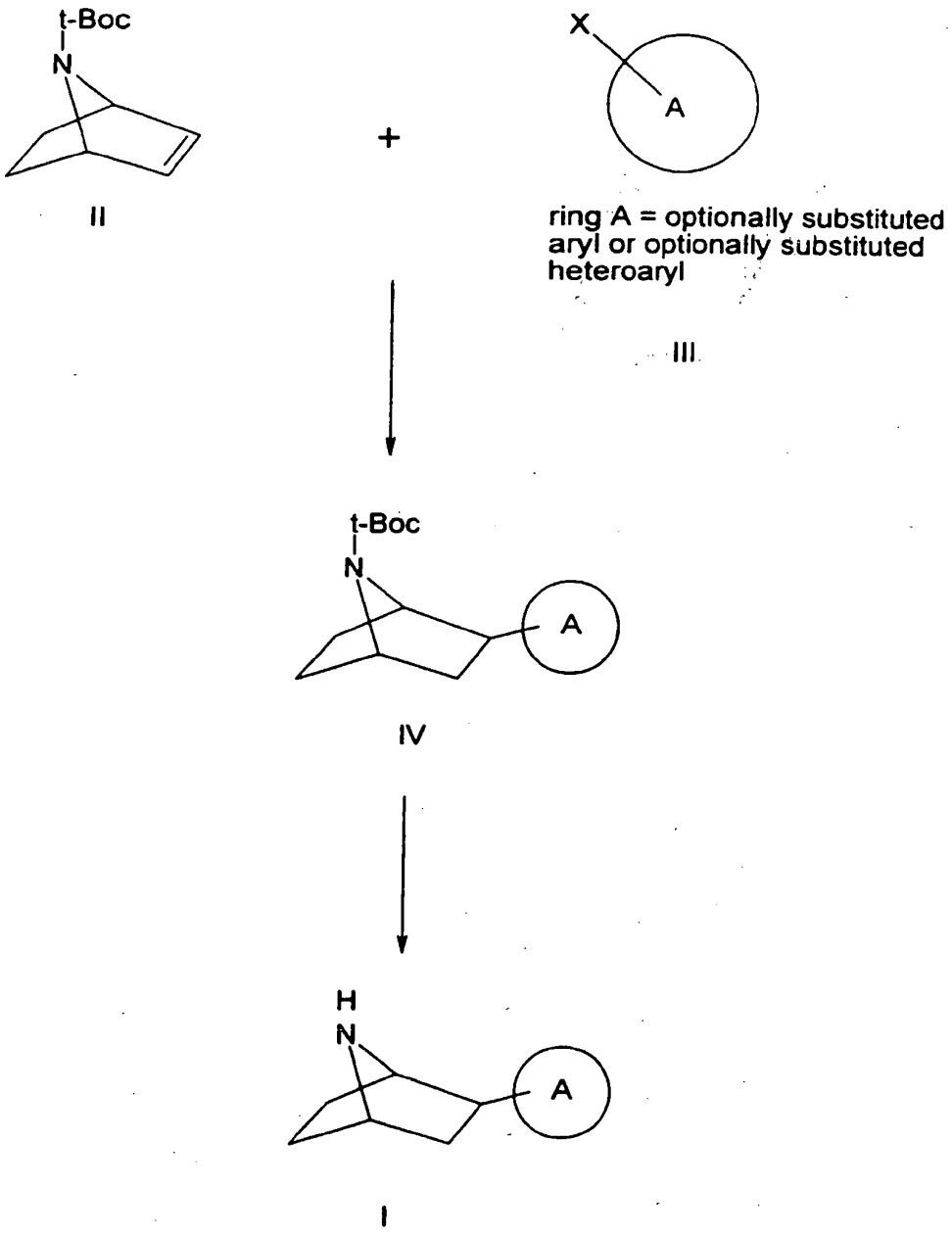
with lead tetraacetate and copper acetate. This reaction is preferably conducted in a reaction inert solvent such as benzene, toluene or xylenes, at a temperature from about room temperature to about the reflux temperature of the

solvent, preferably at about the reflux temperature.

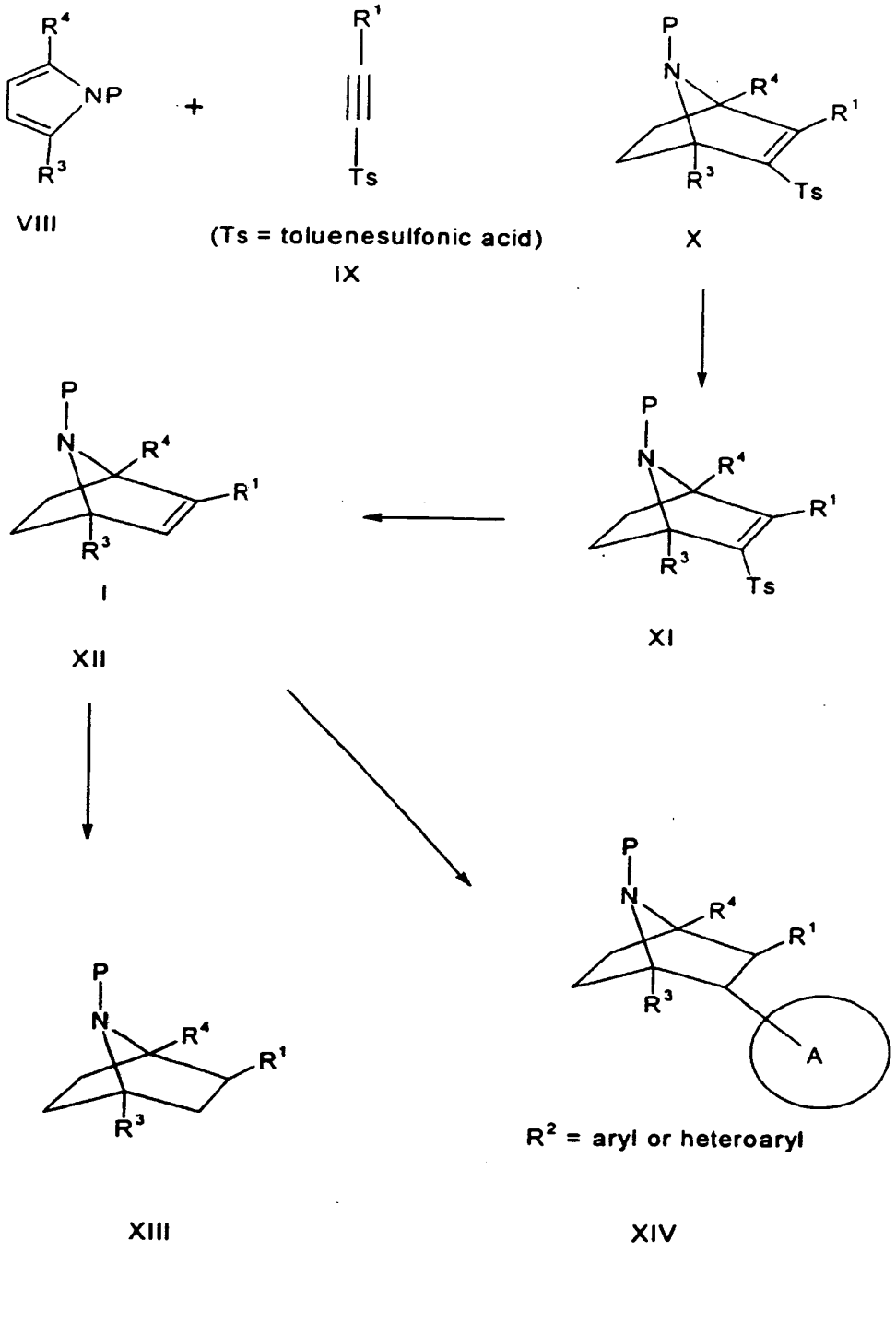
Detailed Description of the Invention

[0024] Except where otherwise stated, R^1 through R^6 and structural formulas I, IX and X in the reaction schemes and discussion that follow are defined as above.

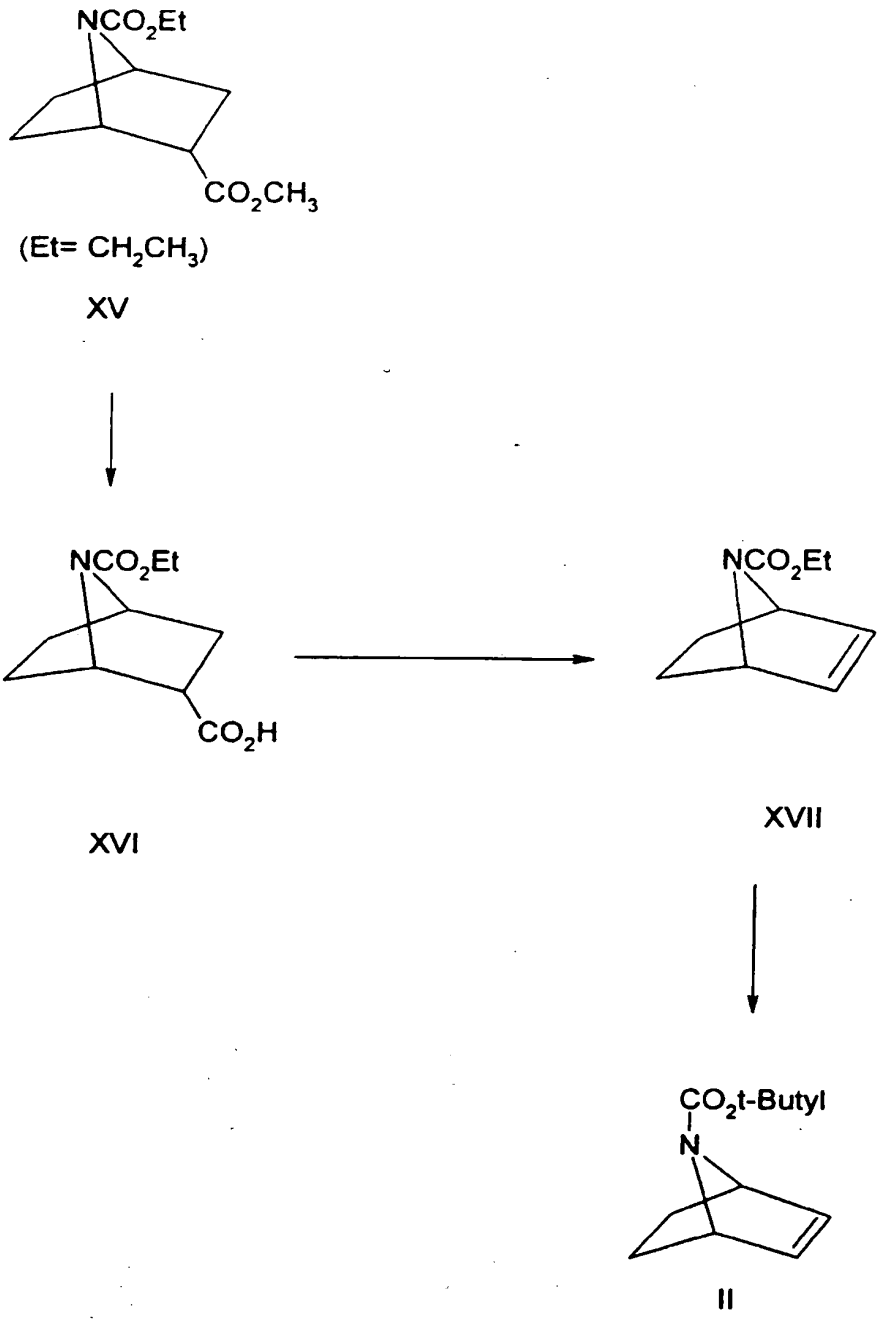
SCHEME 1



SCHEME 2



SCHEME 3



[0025] Scheme 1 illustrates the preparation of compounds of the formula I wherein R^2 is an optionally substituted phenyl or heteroaryl group and all of R^1, R^3 and R^4 are hydrogen. Referring to Scheme 1, the compound of formula II, prepared as illustrated in Scheme 2 and described below, or prepared as described by Altenbach, H. J. et al., Chim. Berichte, 1991, 124, 791-801, is reacted with a compound of the formula III, wherein X is bromine or iodine and ring A is an optionally substituted aryl or heteroaryl group, to form the nitrogen protected compound of formula IV. This reaction, which is a reductive Heck coupling, is typically conducted in a reaction inert polar solvent such as N,N-

dimethylformamide (DMF), THF or acetonitrile, preferably DMF, in the presence of formic acid, a secondary amine base such as piperidine, and a catalytic amount of palladium tetrakistriphenylphosphine or another suitable palladium (O) catalyst. The reaction temperature can range from about 25°C to about 120°C, preferably at the lowest possible temperature at which the aryl or heteroaryl halide will react with the palladium catalyst in a reasonable amount of time. For most reactions, room temperature for 24-72 hours up to about 4-5 days provide the desired reaction conditions, although higher temperatures may be used to increase the rate of reaction.

[0026] Removal of the nitrogen protecting group from the compound of formula IV using standard methods that are well known to those of skilled in the art yields the desired compound of formula I. For example, reaction of the compound of formula IV with hydrochloric acid in ethyl acetate gives the unprotected hydrochloric salt of the corresponding compound of the formula I, and reaction of the compound of formula IV with trfluoroacetic acid in methylene chloride yields the unprotected trifluroacetic acid salt of the same.

[0027] Protecting groups other than t-Boc, which is shown in Schemes 1 and 2, can also be used. Appropriate alternative nitrogen protecting groups (e.g., include $-COCF_3$, $-COCCl_3$, $-COOCH_2CCl_3$, $-COO(C_1-C_6)$alkyl and $-COOCH_2C_6H_5$ and methods of adding and removing them will be obvious to those skill in the art. (See T. W. Green and G. M. Wets, "Protective Group in Organic Synthesis", "1991, John Wiley & Sons, New York, N.Y.).

[0028] The process of Scheme 1 is described in greater detail in United States Patent 5,565,573, which is incorporated herein by reference in its entirety.

[0029] Scheme 2 illustrates a method of preparing all compounds of the formula I, including those which can be prepared using the procedure of Scheme 1. Referring to Scheme 2, a compound of the formula VIII, wherein P is a nitrogen protecting group, is reacted with a compound of the formula IX, wherein Ts is toluenesulfonic acid, to form the corresponding compound of formula X. Alternatively, benzenesulfonic acid may be used instead of toluenesulfonic acid in this reaction. Suitable nitrogen protecting groups will be obvious to those skill in the art (see T. W. Greene and G. M. Wots, "Protective Groups in Organic Synthesis", 1991, John Wiley & Sons, New York, N.Y.) and include (C_1-C_6) alkyl groups and groups having the formula -COR wherein R is $-N(C_1-C_6)$alkyl, (C_1-C_6)alkyl or $-O-(C_1-C_6)$alkyl. This reaction is typically conducted neat at a temperature of about 80°C to about 85°C.

[0030] The compound of formula X that is produced in the foregoing reaction is then converted into the corresponding compound of formula XI by hydrogenating it in an acetonitrile solvent at a temperature from about 15°C to about 90°C, preferably at about room temperature, using methods well known to those of skill in the art (e.g., under a hydrogen gas pressure of about 1-3 atmospheres and using a palladium on carbon (Pd/C) catalyst or other palladium catalyst). Removal of the toluenesulfonic acid or benzenesulfonic acid group from the compound of formula XI yields the corresponding compound of formula XII. This can be accomplished by reacting the compound of formula XI with a sodium mercury amalgam (6%) in methanol and tetrahydrofuran (THF), in the presence of sodium hydrophosphate (Na_2HPO_4) and sodium dihydrophosphate (NaH_2PO_4). Preferably, the reactants are mixed at a temperature of about-78°C and then allowed to warm to room temperature.

[0031] The compound of the formula XII can be converted into the corresponding compound having formula XIII by subjecting it to a hydrogenation reaction as described above. The compound of formula XII can then be converted into the corresponding compound having formula XIV, wherein R^2 is an aryl or heteraryl group, using the methods described above and illustrated in Scheme 1.

[0032] Removal of the nitrogen protecting group from compounds of the formula XIII and XIV, as described above, yields the corresponding final products of formula I.

[0033] Scheme 3 illustrates a method of preparing the t-Boc protected olefin that is the starting material used in the process of Scheme 1. Referring to Scheme 3, the starting material of formula VIII can be obtained as described by D. Bai. et al., J. Org. Chem., 1996, 61: 4600-6. This ester is then hydrolyzed, using methods well known to those of skill in the art, to form the corresponding carboxylic acid of formula IX.

[0034] Reaction of the compound of formula IX with lead tetraacetate and copper acetate yields the compound of formula X. This reaction is generally conducted in a reaction inert solvent such as benzene, toluene, or zylenes, at a temperature from about room temperature to about the reflux temperature of the solvent. It is preferably conducted in benzene at the reflux temperature in an inert atmosphere (e.g., a nitrogen or argon atmosphere).

[0035] The desired nitrogen protected intermediate of formula II can be then be obtained by reacting the compound of formula X with tetramethylsilyl iodide (TMSI) and trifluoroacetic acid, in the presence of triethylamine (TEA), followed by reaction with t-butylpyrocarbonate, also in the presence of TEA. Both these reactions are typically conducted in a reaction inert solvent such as chloroform, methylene chloride, dichloroethane or another chlorinated hydrocarbon solvent, preferably chloroform, at a temperature from about room temperature to about the reflux temperature of the solvent, preferably at the reflux temperature.

[0036] Compounds of the formula I wherein R^6 is (C_1-C_6) alkyl can be prepared from the corresponding compounds wherein R^6 is hydrogen using standard alkylation and reductive amination methods well known to those of skill in the art. (See Jung et al., J.C.S. Chem. Commun., 1984, 10, 630-32; Fletcher et al., J. Org. Chem., 1994 59, 1971-78; Mariano et al., J. A. C. S., 1981, 103, 3148-60, and Gonzales et al., J. A. C. S., 1995, 117, 3405-21).

[0037] Syntheses of olefins identical to that of formula II except that the nitrogen is protected by a protecting group other than t-Boc are described by Altenbach et al., Angew Chem. Suppl., 1982,1614-1221, and by Clayton et al., Tetrahedron Letters, 1993, 34, 7493.

[0038] The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

[0039] The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

[0040] In each of the reactions discussed above, or illustrated in Schemes 1-3, above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, with ambient pressure, i.e., about 1 atmosphere, being preferred as a matter of convenience.

[0041] The compounds of the formula I and their pharmaceutically acceptable salts (hereafter the active compounds") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These compounds are, most desirably, administered in dosages ranging from about 0.25 mg up to about 1500 mg per day, preferably from about 0.25-to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.01 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

[0042] The active compounds can be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More particularly, the active compounds can be administered in a wide variety of different dosage forms, e.g., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight

[0043] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc can be used for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar] as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[0044] For parenteral administration, a solution of an active compound in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

[0045] It is also possible to administer the active compounds topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Biological Assay

[0046] The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites is determined by the following procedure which is a modification of the methods of Lippiello, P. M. and Fernandes, K. G. (in The Binding of L-[^{3}H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes, Molecular Pharm., 29, 448-54, (1986)) and Anderson, D. J. and Americ, S. P. (in Nicotinic Receptor Binding of ^{3}H-Cystisine ^{3}H-Nicotine and ^{3}H-Methylcarmbamylcholine In Rat Brain, European J. Pharm., 253, 261-67 (1994)).

Procedure

[0047] Male Sprague-Dawley rats (200-300 g) from Charles River were housed in groups in hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.-7 p.m. light period). They received standard Purina Rat Chow and water *ad libitum*.

[0048] The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (Molec Pharmacol, 29, 448-454, (1986) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0° in 10 volumes of buffer (w/v) using a Brinkmann Polytron™, setting 6, for 30 seconds. The buffer consisted of 50 mM Tns HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10 minutes; 50,000 x g; 0 to 4°C. The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000 x g; 0 to 4°C. After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0g/100mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$ and has a pH of 7.4 at room temperature.

[0049] Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50µL of vehicle, blank, or test compound solution, respectively. To each tube was added 200 µL of [^{3}H]-nicotine in assay buffer followed by 750 µL of the membrane suspension. The final concentration of nicotine in each tube was 0.9 nM. The final concentration of cytisine in the blank was 1 µM. The vehicle consisted of deionized water containing 30 µL of 1 N acetic acid per 50 mL of water. The test compounds and cytisine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0 to 4° C in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B™ glass fiber filters using a Brandel™ multi-manifold tissue harvester. Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 m each). The filters were then placed in counting vials and mixed vigorously with 20 ml of Ready Safe™ (Beckman) before quantification of radioactivity. Samples were counted in a LKB Wallach Rackbeta™ liquid scintillation counter at 40-50% efficiency. All determinations were in triplicate.

Calculations

[0050] Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytisine (B), i.e.,

$$\text{Specific binding} = (C) = (A) - (B).$$

[0051] Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e., (E) = (D) - (B).

$$\% \text{ Inhibition} = (1-((E)/(C)) \text{ times } 100.$$

[0052] The compounds of the invention that were tested in the above assay exhibited IC_{50} values of less than 1 µM.

[0053] The following experimental examples illustrate, but do not limit the scope of, this invention.

[0054] In the Examples, below, the melting points are not corrected. NMR spectra were recorded on a Varian spectrometer at 400 MHz unless otherwise noted. Spectra chemical shifts are reported in δ relative to chloroform ($CHCl_3$), methanol (CH_3OH), or dimethylsulfoxide (DMSO). IR spectra were obtained as a potassium bromide press. HRMS

was performed by M-Scan Inc. in a matrix of *m*-nitro benzyl alcohol and PEG 200 or 300 using a cesium ion gun.

EXAMPLE 1

2β-(3,4-DIFLUOROPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HYDROCHLORIC ACID SALT

[0055]

A. To a stirred solution of N-t-BOC- azanorbornene (0.4 mmol., 1.0 equivalent (equiv.)) in N,N-dimethylformamide (DMF) (0.4M) under nitrogen gas (N_2) at room temperature (RT), was added piperidine (1.4 mmol., 3.5 equiv.), followed by formic acid (1 mmol., 2.5 equiv.) and 3,4 difluoroiodobenzene (0.6 mmol., 1.5 equiv.). The reaction mixture was stirred until homogeneous and then palladium diacetate di(triphenylphosphine) ($Pd(OAc)_2(Ph_3P)_2$) (0.02 mmol., 0.05 equiv.) was added. The reaction mixture was then purged with N_2 and heated to 80-90°C for fifteen hours whereby a black precipitate formed. The reaction mixture was then partitioned between 100 ml ethyl acetate and 30 ml water (H_2O). The organic layer was then separated and washed, once with 20 ml sodium bicarbonate, twice with 40 ml water and once with 30 ml brine. The organic layer was dried over sodium sulfate (Na_2SO_4), filtered, and the solvents were removed *in vacuo* to yield N-t-BOC-2b-(3,4-difluorophenyl)-7-aza-bicyclo [2.2.1]heptane an oil, which was purified by flash chromatograohy (200 mesh silica, 20g, 96/4 hexanes/ethyl acetate) (42mg/50% yield).

B. The t-BOC protecting group was removed by treatment of the above product with 4 ml of 2.5 M HCl in ethyl acetate at RT for 2.5 hours. Removal of the solvent and excess HCl *in vacuo* results in an oil that is titriated with ethyl acetate to yield white crystals of the title product. (22.5mg/67% yield). MP 206.5-208.5°C.

IR: 2992.7, 2953.8, 2929.1, 2882.0, 2827.2, 2717.0, 2653.3, 2547.4, 1434.1, 1373.1, 1358.9, 1281.1, 1121.1, 888.2, 823.1, 763.4 cm^{-1}.
MS: CI (m/z) 210 ($M+H^+$).
HRMS (m/z) 210.1102, calculated for $C_{12}H_{14}NF_2$, 210.1094.
^1H NMR ($CDCl_3$) δ 9.91(1H, br s), 9.32 (1H, br s), 7.32-7.12 (3H, m), 4.39 (1H, s), 4.08 (1H. d, J=3.5 Hz), 3.1 (1H, dd, J=8.8, 6.7 Hz), 2.35-2.17 (4H, m), 1.81 (1H, ap. t, J=7.1, 11.6Hz), 1.7 (1H, ap. t, J=11.8, 8.5 Hz).
^{13}C NMR ($CDCl_3$) δ 137.5, 123.4, 117.8, 117.6, 117.1, 116.8, 63.8, 58.5, 45.7, 37.1, 28.7, 25.5 .

[0056] The compounds of Examples 2-27 were prepared according the method of Example 1 using the appropriate reactants. The title compounds of Examples 2-51 were prepared using speed analoging technology, as described below. High speed analoging was accomplished in a 96 well plate that used six wells for standards. An automated robot dispensed solutions to a vial in each well. To each vial was added 50 ml of a 0.1M solution of a unique aryl iodide (1.0 equiv.) in N,N-dimethylformamide (DMF). Then 25 ml of a 0.3M solution of azanorbornene in DMF was added, followed by 9 ml a solution that consisted of ammonium formate (1.38M, 2.5 equiv.) and potasium acetate (1.94M, 3.5 equiv.) in water. Lastly, 10 ml of a 0.025M solution of $Pd(OAc)_2(Ph_3P)_2$ in DMF was added. The vials were agitated and heated to 75°C for 20 hours. After cooling down, each vial had 500 ml ethyl acetate added and was filtered through 250 mg of neutral alumina. The vials were dried in a vacuum oven (20 torr/40°C) equipped with a N_2 bleed. The vials were then diluted with 500 ml methanol and aliquots were removed to be analyzed by HPLC and MS. The vials were again dried *in vacuo,* treated with 1 ml of 2.5 M HCl/ethyl acetate for 3 hours at room temperature (RT). The vials were dried under a stream of N_2, followed by drying in a vacuum oven (20 torr/40°C). The vials were diluted in 500 ml methanol and agitated for 20 minutes to dissolve the samples. From each vial was drawn 50 ml to be dispensed onto a microtiter plate with matching 96 wells. Each vial also had an aliquot removed for HPLC and MS testing.

EXAMPLE 2

2β-(3,5-DICHLOROBENZENE)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0057]

MP 198.5-201.5°C.
IR: 2880.0, 2702.0, 2646.5, 2529.4, 1608.0, 1592.8, 1568.4, 1455.3, 1432.7, 1357.4, 1344.8, 892. 859.2, 798.5, 688.9 cm^{-1}.
MS: CI (m/z) 242.1/244.1 ($M+H^+$).
HRMS (m/z) 242.0509, calculated for $C_{12}H_{14}Cl_2N$, 242.0503.
^1H NMR ($CDCl_3$) δ 9.79 (1H, br s), 9.29 (1H, br s), 7.35 (2H, s), 7.19 (1H, s), 4.36 (1H, br s), 4.22 (1H br s), 3.04

(1H br s), 2.31-2.20 (4H, br m), 1.70 (2H, br d J=47.6 Hz).
^{13}C NMR ($CDCl_3$) δ 143.8, 135.4, 127.6, 126.2, 63.3, 58.5, 45.9, 36.9, 28.7 25.5.

EXAMPLE 3

2β-(4-NITROPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0058]

MP 223.0-225.0°C.
IR: 2815.9, 2697.6, 2645.1, 2525.7, 1607.7, 1599.2, 1520.7, 1498.9, 1349.8, 1322.9, 1291.1, 887.3, 857.9, 842.7, 749.9, 701.1 cm^{-1}.
MS: CI (m/z) 219.1 ($M+H^+$).
HRMS (m/z), 219.1150, calculated for $C_{12}H_{15}N_2O_2$, 219.1134.
^1H NMR ($CDCl_3$) δ 9.99 (1H, br s), 9.50 (1H, br s), 8.21 (2H, d J=8.5 Hz), 7.65 (2H, d, J=8.5 Hz), 4.40 (1H, s), 4.20 (1H, s). 3.24 (1H, ap. t, J=8.7, 6.6 Hz), 2.36-2.24 (4H, m), 1.84 (1H, d, J=11.4 Hz), 1.73 (1H, ap.t, t, J=11.8, 6.4 Hz).
^{13}C NMR ($CDCl_3$) δ 147.6, 147.1, 128.6, 124.2, 63.3, 58.6, 46.1, 37.0, 28.8, 25.6.

EXAMPLE 4

2β-(3-THIOPHENE)-7-AZA-BICYCLO[2.2.1]HEPTANE HCL SALT

[0059]

MP 155-157.5°C.
IR: 2818.1, 2649.2, 2626.9, 2540.4, 1609.1, 1598.6, 1464.1, 1452.3, 1369.1, 1349.9, 1333.9, 884.9, 825.6, 786.7, 766.7 cm^{-1}.
MS: CI (m/z) 180.1 ($M+H^+$).
HRMS (m/z) 180.0863, calculated for $C_{10}H_{14}NS$, 180.0847.
^1H NMR ($CDCl_3$) δ 9.99 (1H br s), 9.42 (1H br s), 7.46 (1H, s) 7.28 (1H, t, J=2.46 Hz) 7.13 (1H, d, J=4.91 Hz), 4.37 (1H, s), 4.02 (1H, d J=3.6 Hz), 3.20 (1H, dd, J=9.0, 6.0 Hz), 2.33-2.12 (4H, m), 1.77 (1H, ap. t, J=9.4 Hz, J=12.0 Hz), 1.63 (1H, ap. t, J=9.6, 9.0 Hz).

EXAMPLE 5

2β-(3-FLUORO-4-CHLOROPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0060]

MP 208.5-209.5°C.
IR: 2992.1, 2953.0, 2881.8, 2716.1, 2652.8, 2550.5, 1612.1, 1578.8, 1489.0, 1424.2, 1356.1, 1072.8, 884.4, 818.7, 535.5 cm^{-1}.
MS: CI (m/z) 226.0 ($M+H^+$).
^1H NMR ($CDCl_3$) δ 9.9(1H br s), 9.4 (1H br s), 7.37 (1H, d, J=7.9 Hz), 7.25 (2H, m), 4.37 (1H, s), 4.11 (1H, d, J=3.5 Hz), 3.08 (1H, ap. t, J=6.8, 8.7 Hz), 2.34-2.29 (3H, m), 2.20 (1H, ap. t, J=9.3, 13.3 Hz), 1.81 (1H, ap. t, J=6.8, 11.8 Hz), 1.68 (1H, ap. t, J=12.2, 8.1 Hz).
^{13}C NMR ($CDCl_3$) δ 141.4, 131.0, 123.9, 119.9, 116.2, 63.5, 58.6, 45.7, 36.9, 28.6, 25.5.

EXAMPLE 6

2β-(3-FLOUROPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0061]

MP 211.0-213.5°C.
IR: 2956.7, 2929.1, 2880.6, 2824.6, 2716.4, 2651.9, 2543.4, 2134.8, 1612.38. 1586.32, 1487.9, 1450.1, 1361.2, 1230.6, 1156.8, 893.9, 790.9, 775.4, 690.9 cm^{-1}.

MS: CI (m/z) 191.8 ($M+H^+$).
HRMS (m/z), 192.1186, calculated for $C_{12}H_{15}NF$, 192.1189.
^1H NMR ($CDCl_3$) δ 7.36-7.30 (2H, m), 7.13 (1H, d, J=9.3 Hz), 6.93 (1H, t, J=8.3, 6.6 Hz), 4.39 (1H, s), 4.10 (1H, d, J=3.4 Hz), 3.10 (1H, ap. t, J=9.0, 6.8 Hz), 2.35-2.32 (3H, m), 2.19 (1H, dd, J=13.6, 9.3 Hz), 1.80 (1H, ap. t, J=8.6, 12.0 Hz), 1.68 (1H, ap. t, J=11.3, 6.4 Hz).
^{13}C NMR ($CDCl_3$), δ, 164.2, 142.5, 130.8, 130.7, 122.9, 115.0, 114.8, 114.5, 114.3 63.8, 58.5, 46.3, 37.1, 28.7, 25.5.

EXAMPLE 7

2β-(3-HYDROXYPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0062]

MP 222-224°C.
IR: 3214.5, 2897.6, 2717.7, 2644.0, 2542.7, 1618.2, 1605.1, 1587.9, 1494:7, 1465.8, 1378.1, 1357.3, 1337.0, 1324.9, 1302.9, 1281.7, 1273.9, 1166.5, 1157.2, 931.8, 851.4, 805.5, 780.8, 691.3, 670.2, 514.5, 448.8 cm^{-1}.
MS: CI (m/z) 190.1 ($M+H^+$).
HRMS, 190.1249, calculated for $C_{12}H_{16}NO$, 190.1231.
^1H NMR (d_4 CD_3OD) δ 7.16 (1H, t, J=7.9 Hz), 6.76-6.65 (3H, m), 4.40 (1H, d, J=2.9 Hz), 4.27 (1H, s), 2.34 (1H, dd, J=13.3, 9.5 Hz), 2.09-1.80 (6H, m).
^{13}C NMR (d_4 CD_3OD) δ 157.7, 142.8, 129.6, 117.0, 113.5, 113.3, 63.0, 44.5, 36.3, 27.3, 25.5.

EXAMPLE 8

2β-(3-ACETOPHENONE)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0063]

MP 181.5-183.8°C.
IR: 2996.1, 2962.5, 2840.8, 2791.3, 2697.9, 2639.3, 2528.5, 1678.5, 1602.9, 1581.5, 1362.6, 1295.4, 1279.9, 1260.0, 807.5, 702.3, 689.5 cm^{-1}.
MS: CI (m/z) 215.8 ($M+H^+$).
HRMS, 216.1399, calculated for $C_{14}H_{18}NO$, 216.1388 .
^1H NMR ($CDCl_3$) δ 9.79 (1H, br s), 9.18 (1H, br s), 7.87 (1H, s), 7.78 (1H, d, J=7.26 Hz), 7.69 (1H, d, J=5.77 Hz), 7.43 (1H, d, J=6.84 Hz), 4.38 (1H, br. s), 4.16 (1H, br. s), 3.19 (1H, br. s), 2.60 (3H, s), 2.30-2.20 (4H, m), 1.81 (1H, s), 1.67 (1H, s).
^{13}C NMR ($CDCl_3$) δ 198.4, 141.0, 137.5, 132.1, 129.4, 127.5, 127.4, 63.8, 58.7, 46.2, 36.9, 28.8, 27.1, 25.6.

EXAMPLE 9

2β-(4-TRIFLUOROMETHYLPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT, OIL

[0064]

IR: 2953.5, 2922.3, 2881.2, 2699.0, 2637.8, 2524.6, 1618.0, 1595.2, 1328.7, 1198.0, 1164.3, 1116.3, 1070.3, 1016.7, 887.8, 832.8 cm^{-1}.
MS: CI (m/z) 242.1 ($M+H^+$).
HRMS (m/z) 242.1160, calculated for $C_{13}H_{15}F_3N$, 242.1156.
^1H NMR ($CDCl_3$) δ 9.91 (1H, br s), 9.26 (1H, br s), 7.60 (1H, br s), 4.41 (1H, br s), 4.19 (1H br s), 3.81 (1H, br s), 2.35-2.24 (4H, br m), 1.84 (1H, br s), 1.71 (1H, br s). ^{13}C NMR ($CDCl_3$) d 128.1, 126.0, 64.0, 58.9, 46.5, 37.7, 29.1, 25.8.

EXAMPLE 10

2β-(3-FLUORO-4-METHYLPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE HCL SALT

[0065]

IR: 2879.9, 2822.4, 2690.1, 2650.8, 2543.9, 1609.5, 1577.7, 1508.1, 1372.0, 1352.3, 1326.7, 1274.4, 1251.5, 1118.2, 886.0, 816.4, 757.9, 520.0, 449.4 cm^{-1}.
MS: CI (m/z) 206.1 ($M+H^+$).
HRMS (m/z) 206.1357, calculated for $C_{13}H_{16}FN$, 206.1345.
^1H NMR ($CDCl_3$) δ 10.05 (1H br s), 9.2 (1H br s) 7.17 (2H, s), 7.04 (1H, d, J=10.7 Hz), 4.37 (1H, s), 4.08 (1H, s), 3.06 (1H, br s), 2.34 (4H, br s), 2.20 (3H, s), 1.79 (1H, s), 1.67 (1H, d, J=10.0 Hz).
^{13}C NMR ($CDCl_3$) δ 162.0, 160.0, 140.0, 132.1, 122.5, 114.6, 114.3, 63.9, 58.6, 45.9, 36.9, 28.7, 25.5.

EXAMPLE 11

2β-(3-CHLOROPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE HCL SALT

[0066]

MP 187-189°C.
IR: 2929.5, 2895.2, 2854.2, 2712.2, 2688.0, 2650.5, 2544.7, 1610.5, 1596.0, 1569.9, 1480.7, 1464.4, 1454.6, 1434.3,1347.9, 901.4, 790.0, 696.2 cm^{-1}.
MS: CI (m/z) 207.7, 208.8, 209.7 ($M+H^+$).
HRMS (m/z) 208.0879, calculated for $C_{12}H_{14}ClN$, 208.0893.
^1H NMR ($CDCl_3$) δ 9.90 (1H, br s), 9.21 (1H, br s), 7.45 (1H, d J=7.47 Hz), 7.35-7.20 (3H, m), 4.38 (1H, s), 4.09 (1H, d, J=2.5 Hz), 3.07 (1H, t J=7.8 Hz), 2.34 (3H, br s), 2.18 (1H, dd, J=9.55 Hz, 13.3 Hz), 1.73 (2H, ap dt, J=48.6 Hz, 11.2 Hz, 7.9 Hz).
^{13}C NMR ($CDCl_3$) δ 142.5, 134.6, 130.5, 128.1, 127.6, 125.4, 63.7, 58.6, 46.1, 37.1, 28.8, 25.6.

EXAMPLE 12

2β-(N-BENZYL-5-PYRIDONYL)-7-AZA-BICYCLO[2.2.1]HEPTANE HCL SALT

[0067]

MS: CI (m/z) 281.2 ($M+H^+$).
HRMS (m/z) 281.1661, calculated for $C_{18}H_{21}N_2O_2$, 281.1654.
^1H NMR ($CDCl_3$) δ 9.99 (1H, br s), 9.25 (1H, br s), 7.40-7.24 (7H, m), 6.74 (1H, br s), 5.47 (1H br s), 5.06 (1H, br s), 4.35 (1H, br s), 4.1 (1H, m), 2.65 (1H, br s), 2.31-2.03 (4H, m), 1.80 (1H, br s), 1.66 (1H, br s).

EXAMPLE 13

2β-(N-METHYL-5-PYRIDONYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0068]

IR: 2995.0, 2953.2, 2810.6, 2643.2, 2530.7, 2156.8, 2129.1, 1671.0, 1644.5, 1607.7, 1594.8, 1534.7, 1449.1, 1438.5, 1373.7, 1357.7, 1346.5, 1322.4, 1312.9, 1292.2, 1256.5, 1196.5, 1180.2, 1161.7, 1150.4, 878.7, 835.3, 740.4, 529.0 cm^{-1}.
MS: CI (m/z) 205.1 ($M+H^+$).
HRMS (m/z) 205.1355, calculated for $C_{12}H_{17}N_2O$, 205.1341.
^1H NMR (d_4 CD_3OD) δ 8.34 (1H, s), 8.15 (1H, d, J=8.5 Hz), 7.17 (1H, d, J=8.7 Hz), 4.53 (1H, s), 4.36 (1H, s), 3.94 (3H, s), 3.44 (1H br s), 2.41 (1 H, ap t), 2.20-1.85 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 160.0, 159.0, 139.8, 129.3, 114.4, 62.4, 59.0, 41.9, 39.7, 35.2, 27.2, 25.5.

EXAMPLE 14

2β-(3-FLUORO-5-NITROPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0069]

MP 185.5-187.1°C.
IR: 2960.1, 2881.6, 2842.1, 2709.0, 2650.8, 2533.6, 1606.7, 1534.8, 1455.6, 1348.6, 1319.8, 1283.8, 1235.7, 1155.4, 899.5, 878.6, 870.2, 783.3, 747.7, 685.8 cm^{-1}.
MS: CI (m/z) 237.2 ($M+H^+$).
HRMS (m/z) 237.1, calculated for $C_12H_{14}FN_2O_2$, 237.1039.
^1H NMR ($CDCl_3$) δ 9.80 (1H, br s), 9.54 (1H, br s), 7.98 (1H, s), 7.76-7.71 (2H, m), 4.39 (2H, br s) 3.25 (1H, br s), 2.31 (4H, br s), 1.83 (1H, br s), 1.71 (1H, br s).
^{13}C NMR ($CDCl_3$) δ 163.9, 161.9, 148.2, 144.6, 144.5, 121.2, 121.0, 118.8, 110.3, 110.1, 62.8, 58.6, 45.7, 37.0, 28.6, 25.6.

EXAMPLE 15

2β-(4-AMINOPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0070]

IR: 2874.2, 2566.6, 1975.0, 1598.1, 1572.8, 1512.8, 1468.1, 1344.2, 885.3, 818.2, 541.5, 499.3 cm^{-1}.
MS: CI (m/z) 189.1 ($M+H^+$).
^1H NMR (d_4 CD_3OD) δ 7.53 (2H, d, J=8.4 Hz), 7.43 (2H, d, J= 7.9 Hz), 4.5 (1H, d, J=2.9 Hz), 4.32 (1H, d, J=4.0 Hz), 3.45 (1H, dd, J=9.3, 6.0 Hz), 2.44 (1H, dd, J=13.2, 9.5 Hz), 2.12-1.85 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 144.1, 130.7, 129.8, 124.7, 64.3, 60.5, 45.6, 37.8, 28.9, 26.8.

EXAMPLE 16

2β-(3-FLUORO-4-TRIFLUOROMETHYL-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE HCL SALT

[0071]

MP 228.5-230.0°C.
IR: 2990.7, 2956.7, 2883.6, 2708.8, 2638.3, 2525.5, 1632.1, 1600.2, 1581.8, 1436.3, 1330.5, 1250.5, 1180.6, 1132.9. 1053.1, 834.8, 828.3 cm^{-1}.
MS: CI (m/z) 260.1 ($M+H^+$).
^{1}HRMS (m/z), 260.1050. calculated for $C_{13}H_{14}F_4N$, 260.1062.
^1H NMR ($CDCl_3$) δ 9.81 (1H, br s), 9.31 (1H, br s), 7.62 (1H, t, J=7.6 Hz), 7.44 (1H, d, J=8.1 Hz), 7.31 (1H, d, J=11.2 Hz), 4.40 (1H, s), 4.15 (1H, s), 3.16 (1H, t, J=7.5 Hz), 2.37-2.21 (4H, m), 1.77 (2H, dd, J=11.9, 41.2 Hz).
^{13}C NMR ($CDCl_3$) δ 161.1, 158.5, 147.6, 147.5, 127.7, 127.7, 123.8, 123.3, 121.1, 116.4, 116.2, 63.3, 58.5, 45.9, 36.9, 28.8, 25.5.

EXAMPLE 17

2β-(4-CHLOROPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0072]

IR: 2956.6, 2879.7, 2815.7, 2690.7, 2646.7, 2541.2, 2138.5, 2114.9, 1609.4, 1600.4, 1494.3, 1465.1, 1454.3, 1371.6, 1349.8, 1326.4, 1095.0, 1014.2, 885.8, 824.4, 532.9, 504.5 cm^{-1}.
MS: CI (m/z), 208/210 ($M+H^+$).
^1H NMR, 250 MHz (d_6 DMSO) d 9.0 (2H, br s), 7.40 (4H, s), 4.36 (1H, d, J=3.2Hz), 4.19 (1H br s), 3.26 (1H, dd, J=9.3, 6.4 Hz), 2.28 (1H, dd, J=12.9, 9.6 Hz), 1.99-1.59 (5H, m).
^{13}C NMR (d_6 DMSO) δ 138.9, 133.2, 129.0, 128.9, 63.8, 58.6, 45.8, 36.9, 28.6, 25.5.

Example 18

2β-(3,4-METHYLENEDIOXYPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0073]

MP 220.0-221.5°C.
IR: 2959.7, 2888.7, 2819.2, 2714.1, 2687.6, 2649.0, 2541.7, 1608.6, 1503.4, 1490.3, 1441.7, 1369.6, 1264.0, 1235.3, 1040.5, 930.0, 806.9, 548.4, 524.6, 419.8 cm^{-1}.
MS: CI (m/z) 218 ($M+H^+$).
HRMS (m/z) 218.1185, calculated for $C_{13}H_{16}NO_2$, 218.1181.
^1H NMR, 250 MHz (d_6 DMSO) δ 7.03 (1H, d, J=1.6 Hz), 6.86 (1H, d, J=8.0 Hz), 6.79 (1H, dd, J=8.1, 1.6 Hz), 5.98 (2H, s), 4.25 (1H, d, J=2.9 Hz), 4.16 (1H, s), 3.16 (1H, dd, J=9.2, 6.3 Hz), 2.21 (1H, dd, J=13.0, 9.5 Hz), 1.92-1.61 (5H, m).
^{13}C NMR, 250 MHz (d6 DMSO) δ 147.5, 145.8, 136.0, 120.3, 108.1, 107.8, 100.9, 62.4, 57.9, 44.3, 27.8, 25.2.

EXAMPLE 19

2β-(2-CHLORO-6-METHYL-5-PYRIDINYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0074]

MS CI (m/z) 223, 225 ($M+H^+$).
HRMS (m/z), 223.1011, calculated for $C_{12}H_{16}ClN_2$, 223.1002.
^1H NMR ($CDCl_3$) δ 7.73 (1H, d, J=8.1 Hz), 7.29 (1H, d, J=8.1 Hz), 4.51 (1H, d, J=3.7 Hz), 4.29 (1H, s), 3.50-3.45 (1H, m), 2.58-2.46 (4H, m), 2.08-1 82 (5H, m)

EXAMPLE 20

2β-(4-CYANOPHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0075]

IR: 2938.1, 2878.9, 2858.6, 2831.9, 2741.6, 2721.7, 2693.8, 2649.2, 2556.1, 2532.8, 2230.0, 1609.6, 1508.7, 1376.9, 1349.4, 1327.8, 1301.8, 1182.4, 886.3, 847.9, 837.6, 553.1, 550.4, 537.5 cm^{-1}.
MS: CI (m/z) 199.1 ($M+H^+$).
HRMS (m/z) 199.1255, calculated for $C_{13}H_{15}N_2$, 199.1235.
^1H NMR (d_4 CD_3OD) δ 7.72 (2H, d, J=8.3 Hz), 7.53 (2H, d, J=8.1 Hz), 4.55 (1H, d, J=3.2 Hz), 4.32 (1H, d, J=4.1), 3.47 (1H, dd, , J=9.2, 6.0 Hz). 2.45 (1H, dd, J=13.2, 9.6 Hz), 2.14-1.80 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 146.9, 132.4, 127.7, 138.1, 110.5, 62.5, 59.0, 44.7, 36.3, 27.3, 25.4.

EXAMPLE 21

2β-(3-FLUORO-4-NITRO-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0076]

MP 186.5-188.0°C.
IR: 2955.5, 2881.6, 2851.3, 2694.6, 2641.9, 2545.6, 1612.4, 1600.8, 1524.9, 1511.8, 1345.9, 1325.7, 1248.6, 1061.9, 939.1, 888.7, 833.8, 751.1, 578.2, 547.7, 537.3, 526.1 cm^{-1}.
MS: CI (m/z) 237.1 ($M+H^+$).
HRMS (m/z), 237.1023, calculated for $C_{12}H_{14}FN_2O_2$, 237.1039.
^1H NMR (d_4 CD_3OD) δ 8.09 (1H, t, J=8.1 Hz), 7.46 (1H, d, J=12.5 Hz), 7.36 (1H, d, J=8.1 Hz), 4.59 (1H, s), 4.33 (1H, s), 3.51 (1H, d, J=5.9 Hz), 2.48 (1H, ap. t, J=12.8, 9.9 Hz), 2.07-1.86 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 156.8, 154.1, 149.5,136.0, 126.6, 123.8, 117.9, 117.6, 62.9, 58.5, 45.8, 36.8, 28.6, 25.4.

EXAMPLE 22

2β-(4-AMIDO-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0077]

MP 251.5-253.0°C.
IR: 3363.9, 3160.4, 2989.7, 2950.3, 2879.0, 2856.1, 2782.2, 2701.3, 2652.7, 2638.0, 2524.9, 1671.3, 1658.2, 1623.0, 1611.4, 1599.3, 1560.0, 1416.7, 1398.2, 1374.0, 888.1, 850.7, 778.0, 760.0, 747.4, 625.6, 606.7, 532.2, 473.2 cm^{-1}.
MS: CI (m/z), 217.1 ($M+H^+$).
^1H NMR (d_4 CD_3OD) δ 7.87 (2H, d, J=8.5 Hz), 7.41 (2H, d, J=8.1 Hz), 4.52 (1H, s), 4.29 (1H, s), 3.45 (1H, ap. t, J=6.0, 3.3 Hz), 2.42 (1H, ap. t, J=9.8, 3.5 Hz), 2.05-1.88 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 172.1, 147.2, 133.1, 129.5, 128.2, 64.2, 60.5, 46.0, 37.8, 28.9, 26.9.

EXAMPLE 23

2β-(3-FLUORO-4-AMINO-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0078]

MP 266.0-270.0 °C.
IR: 2988.3, 2819.9, 2639.1, 2539.0, 2001.5, 1608.2, 1598.5, 1568.9, 1555.2, 1510.1, 1424.3, 1369.6, 1340.9, 1268.8, 1254.8, 893.5, 884.2, 837.4, 470.5, 452.6 cm^{-1}.
MS: CI (m/z) 207.1 ($M+H^+$).
HRMS (m/z) 207.1290, calculated for $C_{12}H_{16}FN_2$, 207.1297.
^1H NMR (d_4 CD_3OD) δ 7.46-7.39 (2H, m), 7.29 (1H, d, J=8.4 Hz), 4.51 (1H, s), 4.3 (1H, s), 3.44 (1H, dd, J=9.5, 5.9 Hz), 2.43 (1H, dd, J=13.2, 9.9 Hz), 2.09-1.86 (5H, m).

Example 24

2β-(4-SULFONAMIDO-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0079]

MP 245.5-247.0°C.
IR: 3223.5, 3188.5, 3024.0, 2956.7, 2862.6, 2826.1, 2695.1, 2646.9, 2531.0, 1607.4, 1327.6, 1152.3, 1099.1, 912.1, 888.4, 832.5, 679.2, 617.2, 579.0, 558.4, 548.0, 516.9 cm^{-1}.
MS: CI (m/z) 253.1.
^1H NMR (d_4 CD_3OD) δ 7.88 (2H, d, J=8.4 Hz), 7.51 (2H, d, J=8.4 Hz), 4.55 (1H, d, J=3.0 Hz), 4.31 (1H, d, J=4.0 Hz), 3.48 (1H, dd, J=9.2, 6.2 Hz), 2.45 (1H, dd, J=13.4, 9.7 Hz), 2.11-1.86(5H, m).

EXAMPLE 25

2β-(3-METHYL-5-ISOXZAZOLE)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0080]

MP 172.5-178.0°C.
IR: 2959.2, 2842.3, 2802.6, 2705.7, 2691.1, 2666.7, 2639.7, 2529.7, 1606.0, 1465.6, 1442.0, 1415.0, 1374.2, 1355.3, 1149.3, 890.9, 887.7, 824.0, 529.4 cm^{-1}.
MS: CI (m/z), 179 ($M+H^+$).
HRMS, 179, 1177, calculated for $C_{10}H_{14}N_2O$, 179. 1184.
^1H NMR ($CDCl_3$) δ 10.11 (1H, br s), 9.19 (1H, s), 6.42 (1H, s), 4.38 (1H, s), 4.24 (1H, s), 3.26 (1H, ap. t, J=8.3, 6.23 Hz), 2.32-2.16 (7H, m), 1.74 (2H, dd, J=29.4, 10.8 Hz).
^{13}C NMR ($CDCl_3$) δ 170.7, 160.2, 103.5, 63.1, 62.0, 58.2, 38.5, 36.8, 35.1, 27.7, 25.4, 11.5.

EXAMPLE 26

2β-(3-METHYL-5-ISOXZAZOLE)-7-AZA-BICYCLO[2.2.1]HEPTANE, N-METHYL

[0081]

MS CI (m/z), 193 ($M+H^+$).
^1H NMR ($CDCl_3$) δ 5.91 (1H, s), 3.46 (1H, d, J=3.7 Hz), 3.37 (1H, t, J=4.2 Hz), 2.87 (1H, dd, J=9.0, 5.1 Hz), 2.26 (3H, s), 2.25 (3H, s), 1.98-1.83 (4H, m), 1.53-1.39 (2H, m).

EXAMPLE 27

2β-(3-METHYL-5-ISOXZAZOLE)-7-AZA-BICYCLO[2.2.1]HEPTANE, N-ACETYL

[0082]

MS: CI (m/z), 221 ($M+H^+$), 238 ($M+NH_4^+$).
^{13}C NMR ($CDCl_3$) δ 174.6, 174.4, 167.5, 166.8, 159.8, 101.9, 100.6, 61.0, 56.8, 56.4, 52.6, 41.6, 40.1, 38.4, 36.1, 29.9, 28.4, 28.3, 21.4, 11.4.

EXAMPLE 28

2B-(3,4-DIFLUOROPHENYL)-7-AZABICYCLO[2.2.1]HEPTANE, HCL SALT

[0083]

MP 206.5-208.5°C.
IR: (KBr), 2992.7, 2953.8, 2929.1, 2882.0, 2827.2, 2717.0, 2653.3, 2547.4, 1434.1, 1373.1, 1358.9, 1281.1, 1121.1, 888.2, 823.1, 763.4 cm^{-1}.
MS: CI (m/z) 210 ($M+H^+$).
HRMS (m/z) 210.1102, calculated for $C_{12}H_{14}NF_2$, 210.1094.
^1H NMR ($CDCl_3$) δ 9.91(1H, br s), 9.32 (1H, br s), 7.32-7.12 (3H, m), 4.39 (1H, s), 4.08 (1H, d, J=3.5 Hz), 3.1 (1H, dd, J=8.8, 6.7 Hz), 2.35-2.17 (4H, m), 1.81 (1H, ap. t, J=7.1, 11.6 Hz), 1.7 (1H, ap. t, J=11.8, 8.5 Hz).
^{13}C NMR ($CDCl_3$) δ 137.5, 123.4, 117.8, 117.6, 117.1, 116.8, 63.8, 58.5, 45.7, 37.1, 28.7, 25.5.

EXAMPLE 29

4-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-BENZAMIDINE HCL SALT

[0084]

MP 198.5-201.0°C.
IR: (KBr), 3031.3, 2911.0, 2844.1, 2707.5, 2643.8, 2527.3, 1677.2, 1612.3, 1600.4, 1480.5, 1470.6, 1446.3, 1409.7, 1366.1, 1343.0, 1324.9, 1159.8, 886.2, 833.1, 756.3, 738.1, 684.1, 634.7, 528.0 cm^{-1}.
MS: CI (m/z) 216.2 ($M+H^+$).
HRMS (m/z), 216.1505, calculated for $C_{13}H_{18}N_3$, 216.1501.
^1H NMR (d4 CD40D) δ 7.82 (2H, d, J=8.1 Hz), 7.59 (2H, d, J=8.3 Hz), 4.56 (1H, d, J=3.7 Hz), 4.33 (1H, br. s), 3.51 (1H, dd, J=6.0, 9.5 Hz), 2.47 (1H, dd, J=13.4, 9.5 Hz), 2.08-1.89 (5H, m).
^{13}C NMR (d_4, CD_4OD) δ 149.7, 129.6, 129.0, 64.0, 60.4, 46.0, 37.8, 28.9, 26.8 .

EXAMPLE 30

2-(4-METHANESULFONYL-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0085]

MP 242.5-244.0°C.
IR: (KBr), 3015.1, 2993.2, 2949.8, 2929.8, 2874.1, 2812.3, 2701.8, 2644.7, 2531.6, 1360.7, 1597.8, 1360.7,

1324.3, 1302.8, 1289.8, 1169.3, 1146.6, 1087.6, 954.0, 826.9, 776.7, 560.7, 534.6, 523.6, 488.1 cm^{-1}.
MS: CI (m/z) 252.1 ($M+H^+$).
HRMS (m/z), 252.1081, calculated $C_{13}H_{18}NOS$, 252.1058.
^1H NMR (d_4 CD_3OD) δ 7.94 (2H, d, J=8.3 Hz), 7.59 (2H, d, J=8.3 Hz), 4.57 (1H, d, J=3.7 Hz), 4.32 (1H, br. s), 3.51 (1H, dd, J=9.3, 5.8 Hz), 3.10 (3H, s), 2.47 (1H, dd, J=13.4, 9.7 Hz), 2.11-1.68 (5H, m).
^{13}C NMR (d_4CD_3OD) δ 149.2, 140.8, 129.1, 129.0, 64.0, 60.5, 46.0, 44.4, 37.8, 28.8, 26.8.

EXAMPLE 31

4-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-PHENOL HCL SALT

[0086]

MP 242.5-244.0°C.
IR: (KBr), 3162.0, 3106.4, 3010.9, 2982.8, 2967.3, 2953.9, 2881.1, 2830.4, 2697.8, 2657.5, 2577.4, 2530.5, 1614.2, 1605.2, 1589.5, 1518.1, 1460.6, 1448.1, 1439.6, 1355.5, 1333.0, 1308.4, 1268.9, 1252.1, 1242.1, 1229.9, 1191.7, 1162.2, 1154.1, 892.7, 840.0, 828.1, 706.8, 509.9 cm^{-1}.
MS: CI (m/z) 190.2 ($M+H^+$); HRMS (m/z), 190.1214, calculated for $C_{12}H_{16}NO$, 190.1232.
^1H NMR (d_4 CD_3OD) δ 7.11 (2H, d, J=8.0 Hz), 6.77 (2H, d, J=7.7 Hz), 4.34 (1H, d, J=2.3Hz), 4.27 (1H, br s), 2.32 (1H, dd J=13.4, 9.4 Hz), 2.11-1.82 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 156.2, 131.8, 130.7, 127.4, 115.2, 63.6, 59.0, 44.1, 36.2, 27.3, 25.5.

EXAMPLE 32

2-(4-METHYLSULFANYL-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE HCL SALT

[0087]

MP 216.5-218.0°C.
IR: (KBr), 3021.7, 2992.9, 2979.5, 2958.1, 2874.2, 2853.7, 2821.8, 2716.1, 2689.7, 2651.6, 2550.7, 2535.3, 2138.4, 1609.4, 1497.2, 1465.0, 1453.2, 1439.2, 1427.5, 1371.6, 1355.0, 1327.1, 1095.8, 1016.4, 974.8, 887.7, 820.4, 790.2, 534.1, 506.0 cm^{-1}.
MS:CI (m/z) 220.2 ($M+H^+$).
HRMS (m/z), 220.1174, calculated for $C_{13}H_{18}NS$, 220.1160.
^1H NMR (d_4CD_3OD) δ 7.28-7.22 (4H, m), 4.41 (1H, d, J=2.3 Hz), 4.29 (1H, br. s), 3.33 (1H, dd, J=9.1, 5.8 Hz), 2.44 (3H, s), (1H, dd, J=13.0, 9.6 Hz), 2.10-1.83 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 128.0, 127.6, 64.2, 60.2, 45.1, 37.9, 28.8, 26.8.

EXAMPLE 33

4-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-BENZOIC ACID METHYL ESTER HCL SALT

[0088]

IR: (KBr), 2995.9, 2983.0, 2959.8, 2906.0, 2882.8, 2850.0, 2812.8, 2713.2, 2686.8, 2649.6, 2622.6, 2533.5, 1726.3, 1608.0, 1464.0, 1457.6, 1436.7, 1417.9, 1371.4, 1348.7, 1326.6, 1279.5, 1191.7, 1140.6, 1106.2, 1018.5, 959.0, 892.0, 842.7, 776.0, 761.6, 705.9, 536.0, 511.2 cm^{-1}.
MP: 235.0-236.0C.
MS: CI (m/z) 232.2 ($M+H^+$).
HRMS (m/z), 232.1348, calculated for $C_{14}H_{18}NO_2$, 232.1337.
^1H NMR (d_4 CD_3OD) δ 8.00 (2H, d, J=8.1 Hz), 7.43 (2H, d, J=8.5 Hz), 4.53 (1H, d, J=7.1 Hz), 4.29 (1H, s), 3.88 (3H, s), 3.48-3.44 (1H, m), 2.44 (1H, dd, J=13.3, 9.8 Hz), 2.11-1.85 (5H, m).
^{13}C NMR ($CDCl_3$) δ 166.8, 145.4, 130.2, 129.0, 127.5, 63.4, 58.5, 52.0, 46.3, 36.9, 28.7, 25.5.

EXAMPLE 34

4-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-BENZOIC ACID HCL SALT

[0089]

MP 261.5-264.5 °C.
IR: (KBr), 3090.6, 3038.8, 2980.8, 2956.9, 2932.8, 2884.7, 2699.0, 26415, 2576.3, 2507.9, 1682.2, 1607.3, 1573.6, 1467.4, 1421.9, 1403.3, 1371.6, 1354.1, 1322.2, 1308.7, 1296.2, 1264.2, 1222.7, 1155.5, 1125.8, 1112.9, 887.9, 850.8, 830.5, 776.5, 766.4, 711.2, 696.1, 529.4, 506.7 cm^{-1}.
MS: CI (m/z) 218.2 ($M+H^+$).
HRMS (m/z) 218.1181, calculated for $C_{13}H_{16}NO_2$, 218.1181.
^1H NMR (d_4 CD_3OD) δ 8.01 (2H, d, J=8.1 Hz), 7.42 (2H, d, J=8.5 Hz), 4.54 (1H, d, J=2.9 Hz), 4.30 (1H, s), 3.46 (1H, dd, J=9.2, 6.3 Hz), 2.44 (1H, dd, J=13.4, 9.6 Hz), 2.12-1.86 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 168.5, 146.9, 130.2, 126.9, 63.0, 59.3, 44.9, 36.7, 27.7, 25.8.

EXAMPLE 35

2-(3-FLUORO-4-TETRAZOL-1-YL-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE HCL SALT

[0090]

MP: decomposes 231°C dec.
IR: (KBr), 3082.8, 3012.2, 2988.2, 2963.7, 2941.3, 2881.4, 2842.4, 2826.9, 2803.8, 2720.2, 2706.0, 2659.9, 2640.8, 2540.5, 2529.3, 2493.5, 2382.8, 1603.4, 1527.5, 1465.4, 1453.8, 1402.7, 1373.0, 1239.7, 1214.9, 1172.6, 1146.9, 1085.9, 993.5, 897.4, 830.5, 622.8, 540.2, 523.7, 404.3 cm^{-1}.
MS: CI (m/z) 260.3 ($M+H^+$).
HRMS (m/z), 260.1317, calculated for $C_{13}H_{15}N_5F$, 260.1311.
^1H NMR (d_4 CD_3OD) δ 9.61 (1H, d, J=1.7 Hz), 7.87 (1H, t, J=8.1Hz), 7.52 (1H, d, J=11.8 Hz), 7.41 (1H, d, J=8.3 Hz), 4.57 (1H, d, J=3.5 Hz), 4.32 (1H, s), 3.52 (1H, dd, J=9.2, 6.1 Hz), 2.48 (1H, dd, J=13.4, 9.6 Hz), 2.13-1.86 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 156.0, 153.5, 143.9, 143.8, 125.8, 124.2, 115.9, 115.7, 62.9, 59.3, 44.5, 36.6, 27.6, 25.7.

EXAMPLE 36

2-(4-NITRO-3-TRIFLUOROMETHYL-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE HCL SALT

[0091]

IR: (KBr), 2956.9, 2882.3, 2814.2, 2707.1, 2642.7, 2531.1, 1602.6, 1539.4, 1495.2, 1469.2, 1454.3, 1421.1, 1362.0, 1323.6, 1282.8, 1212.2, 1177.9, 1142.9, 1048.3, 906.5, 869, 857.4, 841.8, 822.6 cm^{-1}.
MS: CI (m/z), 287.2 ($M+H^+$).
HRMS (m/z) 287.1016, calculated for $C_{13}H_{14}F_3N_2O_2$, 287.1007.
^1H NMR ($CDCl_3$) δ 10.15 (1H, br. s), 9.79 (1H, br. s), 8.11 (1H, d, J=8.3 Hz), 7.95 (1H, d, J=8.3 Hz), 7.72 (1H, s), 4.42 (1H, br. s), 4.20 (1H, br. s), 3.29 (1H, ap. t, J=8.5, 7.3 Hz), 2.37-2.29 (4H, m), (2H, dd, J=45.8, 10.3 Hz).
^{13}C NMR ($CDCl_3$) δ 146.0, 145.7, 131.9, 127.93, 127.89, 126.0, 123.6, 63.1, 58.4, 46.0, 36.8, 28.7, 25.4.

EXAMPLE 37

2-[3-FLUORO-4-(5-TRIFLUOROMETHYL-TETRAZOL-1-YL)-PHENYL]-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0092]

MP 195.5-198.5°C.
IR (KBr), 2988.4, 2955.7, 2882.2, 2703.2, 2639.7, 2529.1, 1620.3, 1603.3, 1538.7, 1517.9, 1469.5, 1452.9, 1436.9, 1358.1, 1322.5, 1279.8, 1247.2, 1220.4, 1173.7, 1136.8, 1106.5, 1059.3, 1037.7, 1016.9, 982.0, 937.0, 883.9, 830.4, 823.9, 772.4, 757.5, 638.6, 532.0, 497.3 cm^{-1}.

MS: CI (m/z) 328.1 ($M+H^+$).
HRMS (m/z) 328.1185, calculated for $C_{14}H_{14}N_5F_4$, 328.1185.
^1H NMR (d_4 CD_3OD) δ 7.74 (1H, t, J=8.0), 7.59 (1H, dd, J=11.2, 1.7 Hz), 7.49 (1H, dd, J=8.3, 0.8 Hz), 4.63 (1H, d, J=3.7 Hz), 4.34 (1H, ap. t, J=4.4, 3.7), 3.58 (1H, dd, J=9.5, 6.1 Hz), 2.52 (1H, dd, J=13.4, 9.7 Hz), 2.17-1.88 (5H.m).
^{13}C NMR ($CDCl_3$) δ 175.7, 157.5, 154.9, 147.8, 128.4, 124.6, 119.4, 119.3, 117.0, 116.8, 63.4, 58.7, 46.1, 37.1, 28.8, 25.4.

EXAMPLE 38

2-(3-CHLORO-4-NITRO-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0093]

MP 242.5-244.5°C.
IR: (KBr), 3104.1, 3040.4, 3020.0, 2995.1, 2961.2, 2863.3, 2842.6, 2794.1, 2685.3, 2642.8, 2609.5, 2587.1, 2575.8, 2526.9, 2384.2, 1609.0, 1593.6, 1584.2, 1520.0, 1478.5, 1466.4, 1342.8, 1322.9, 1303.4, 1292.1, 1280.1, 1271.8, 1254.3. 1234.3, 1214.5, 1165.0, 1139.3, 1060.0, 1049.0, 930.8, 905.1, 882.0, 865.3, 842.5, 816.7, 750.0, 704.9, 693.2, 531.5, 447.1 cm^{-1}.
MS: CI ($M+H^+$) m/z=253.1/255.1.
HRMS (m/z) 253.0741, calculated for $C_{12}H_{13}ClN_2O_2$, 253.0744.
^1H NMR (d_4 CD_3OD) δ 7.93 (1H, d, J=8.5 Hz), 7.67 (1H, d, J=1.7 Hz), 7.47 (1H, dd, J=8.5, 1.9 Hz), 4.57 (1H, d, J=3.5 Hz), 4.31 (1H, ap. t, J=3.9, 4.4 Hz), 3.49 (1H, dd, J=9.5, 6.2 Hz), 2.46 (1H. dd, J=9.8, 13.5 Hz), 2.07-1.85 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 148.1, 130.2, 126.7, 125.9, 62.6, 59.2, 44.4, 36.6, 27.6, 25.6.

EXAMPLE 39

2-(4-TETRAZOL-1-YL-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0094]

IR: (KBr), 3070.4, 2967.1, 2952.1, 2914.5, 2877.0, 2745.9, 2711.5, 2673.5, 2650.7, 2547.0, 1601.5, 1524.0, 1469.8, 1398.0, 1374.9, 1362.7, 1346.7, 1328.7, 1322.5, 1313.2, 1252.1, 1217.1, 1193.9, 1183.3, 1091.6, 1057.2, 1041.8, 995.4, 907.7, 890.2, 856.7, 834.6, 812.6, 538.2, 522.2 cm^{-1}.
MS: CI ($M+H^+$) m/z=242.1.
HRMS (m/z) 242.1421, calculated for $C_{13}H_{16}N_5$, 242.1406.
^1H NMR (d_4 CD_3OD) δ 9.77 (1H, s), 7.88 (2H, d, J=8.1 Hz), 7.60 (2H, d, J=8.1 Hz), 4.57 (1H, br. s), 4.34 (1H, br. s), 3.51 (1H, ap. t, J=8.5, 6.4 Hz), 2.48 (1H, dd, J=9.9, 13.0 Hz), 2.16-1.88 (5H, m).

EXAMPLE 40

2-(6-METHOXY-PYRIDIN-2-YL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0095]

MS CI ($M+H^+$), (m/z)=205.1.
HRMS (m/z) 205.1343, calculated for $C_{12}H_{17}N_2O$, 205.1341.
^1H NMR (d_4 CD_3OD) δ 7.62 (1H, t, J=7.8 Hz), 6.85 (1H, d, J=7.3 Hz), 6.69 (1H, d, J=8.3 Hz), 4.36 (2H, m), 3.36 (1H, dd, J=9.2, 4.0 Hz), 2.30 (1H, dd, J=13.3, 9.5 Hz), 2.06-1.85 (5H, m).
^{13}C NMR (d_4 CD_3OD) δ 145.5, 115.4, 109.3, 62.8, 58.9, 56.0, 44.1, 35.4, 26.8, 26.0.

EXAMPLE 41

2-(4-METHANESULFINYL-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE. HCL SALT

[0096]

IR: (KBr), 2978.6, 2952.2, 2883.7, 2840.5, 2700.9, 2643.4, 2528.2, 1688.8, 1601.1, 1497.0, 1466.8, 1413.9, 1366.3, 1325.4, 1297.8, 1220.1, 1199.4, 1173.9, 1159.1, 1089.8, 1046.1, 1012.1, 956.6, 888.0, 826.0, 538.8, 519.6, 480.2 cm^{-1}.
MS: CI ($M+H^+$), m/z=236.1.
HRMS (m/z) 236.1103, calculated for $C_{13}H_{18}NOS$, 236.1109.
^1H NMR ($CDCl_3$) δ 7.66 (4H, br s), 4.42 (1H, br s), 4.14 (1H, br s), 3.20 (1H br s), 2.71 (3H, s), 2.39-2.26 (4H, m), 1.87-1.73 (2H, m).
^{13}C NMR (d_4 CD_3OD) δ 145.5, 143.9, 128.1, 124.4, 63.1, 59.3, 44.8, 42.7, 36.7, 27.7, 25.8.

EXAMPLE 42

2-(4-BROMO-3-FLUORO-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0097]

MP 195.7-197.3°C.
IR (KBr): 2992.5, 2956.9, 2879.5, 2858.3, 2823.7, 2714.2, 2690.3, 2651.1, 2544.8, 1610.2. 1587.8, 1577.0, 1486.4, 1465.1. 1454.6, 1419.4, 1372.0, 1353.3, 1327.0, 1305.9, 1279.4. 1242.2, 1230.6, 1170.6, 1154.0, 1067.8, 1042.7, 982.7, 884.0, 812.5, 773.5, 767.6, 695.2, 547.4, 532.0 cm^{-1}.
MS: CI ($M+H^+$), m/z=270.1/272.0.
HRMS (m/z) 270.0298, calculated for $C_{12}H_{14}BrFN$, 270.0293.
^1H NMR (d_4 CD_3OD) δ 7.60 (1H, t, J=7.8 Hz), 7.24 (1H, d, 9.8 Hz), 7.07 (1H, d, J=8.5 Hz), 4.48 (1H, br s), 4.28 (1H, br s), 3.38 (1H, ap. t, J=5.8, 9.3 Hz), 2.41 (1H, dd, J=13.4, 9.9 Hz), 2.04-1.83 (5H, m).

EXAMPLE 43

2-(4-CYANO-3-FLUORO-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0098]

MP 98.7-99.8°C.
IR: (KBr) 3086.8, 3063.6, 3034.4, 2998.3, 2987.6, 2957.3, 2883.0, 2844.3, 2810.8, 2735.6, 2707.1, 2669.7, 2642.7, 2529.7, 2235.3, 1623.1, 1601.9, 1568.1, 1507.0, 1467.4, 1451.0, 1433.7, 1373.4, 1356.8, 1326.9, 1314.9, 1297.6, 1262.7, 1252.9, 1228.4, 1183.7, 1165.2, 1153.2, 1116.9, 1060.9, 938.3, 891.9, 824.1, 809.0, 736.4, 521.1, 506.5 cm^{-1}.
MS: CI ($M+H^+$), m/z=217.
HRMS (m/z) 217.1158, calculated for $C_{13}H_{14}FN_2$, 217.1141.
^1H NMR (d_4 CD_3OD) δ 7.74 (1H, t, J=7.6 Hz), 7.39 (1H, d, J=10.8 Hz), 7.32 (1H, dd, J=8.1, 1.7 Hz), 4.55 (1H, d, J=3.5 Hz), 4.30 (1H, t, J=3.9 Hz), 3.49 (1H, dd, J=9.6, 6.0 Hz), 2.45 (1H, dd, J=13.3, 9.8 Hz), 2.07-1.84 (5H, m).

EXAMPLE 44

2-(3,4,5-TRIFLUORO-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT.

[0099]

MP 186.0-189.0°C.
IR: (KBr) 3014.2, 2963.0, 2866.0, 2831.6, 2699.0, 2646.3, 2614.4, 2584.9, 2537.7, 1619.2, 1609.6, 1532.9, 1458.1, 1447.2, 1373.3, 1352.6, 1321.5, 1312.8, 1275.2, 1240.4, 1224.5, 1173.5, 1158.0, 1068.6, 1041.4, 1020.8, 895.7, 881.8, 846.3, 789.3, 733.9, 533.6 cm^{-1}.
MS: CI ($M+H^+$) 228.
HRMS (m/z) 228.1004, calculated for $C_{12}H_{13}F_3N$, 228.1000.

^{1}H NMR ($CDCl_3$) δ 9.99 (1H, br s), 9.54 (1H, br s), 7.17 (2H, t, J=7.4 Hz), 4.39 (1H, br s), 4.13 (1H, br s), 3.05 (1H, dd, J=7.9, 7.3 Hz), 2.34-2.17 (4H, m), 1.80-1.66 (2H, m).
^{13}C NMR ($CDCl_3$) δ 152.4, 149.9, 112.1, 111.8, 63.2, 58.4, 45.5, 36.9, 28.4, 25.3.

EXAMPLE 45

2-(3,4,5-TRIMETHOXY-PHENYL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0100]

MP 255.5-270.0°C.
IR: (KBr) 2995.2, 2960.2, 2944.1, 2929.4, 2844.5, 2811.5, 2711.7, 2671.3, 2524.3, 2499.2, 1593.2, 1511.3, 1465.8, 1430.1, 1369.3, 1338.7, 1326.9, 1278.4, 1250.6, 1238.4, 1184.9, 1156.9, 1148.2, 1131.3, 1011.9, 1000.2, 945.9, 828.7, 733.0, 529.4, 510.5 cm^{-1}.
MS: CI ($M+H^+$) 264.2.
^{1}H NMR (CD_3OD) δ 6.58 (2H, s), 4.42 (1H, d, J=3.3 Hz), 4.27 (1H, d, J=3.9 Hz), 3.85 (6H, d, J=1.0 Hz), 3.71 (3H, d, J=1.2 Hz), 3.32 (1H, dd, J=6.1, 9.4 Hz), 2.36 (1H, dd, J=9.5, 13.5 Hz), 2.10-1.84 (5H, m).
^{13}C NMR δ 154.8, 138.8, 138.0, 105.4, 64.8, 61.1, 60.4, 56.9, 46.4, 37.8, 28.8, 26.8.

EXAMPLE 46

2-(5-NITRO-FURAN-2-YL)-7-AZA-BICYCLO[2.2.1]HEPTANE, HCL SALT

[0101]

IR: (KBr) 3077.6, 3053.6, 2997.2, 2957.7, 2915.3, 2883.4, 2854.7, 2823.4, 2692.2, 2650.0, 2523.9, 1605.6, 1586.8, 1528.2, 1517.1, 1494.2, 1467.5, 1454.3, 1384.9, 1357.1, 1326.0, 1248.3, 1222.3, 1157.0, 1034.7, 809.8, 741.8 cm^{-1}.
MS: CI ($M+H^+$) m/z=209.1.
HRMS (m/z) 209.0912, calculated for $C_{10}H_{13}N_2O_3$, 209.0926.
^{1}H NMR (CD_3OD) δ 7.40 (1H, d, J=3.5 Hz), 6.65 (1H, d, J=3.5 Hz), 4.51 (1H, d, J=3.5 Hz), 4.33 (1H, s), 3.52 (1H, dd, J=9.2, 5.5 Hz), 2.34 (1H, dd, J=13.5, 9.6 Hz), 2.22-2.19 (1H, m), 2.05-1.82 (4H, m).

EXAMPLE 47

5-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-3-METHYL-BENZO[D]ISOXAZOLE, HCL SALT

[0102]

MP: decomposes 267°C.
IR: (KBr), 2994.5, 2963.7, 2856.0, 2839.6, 2783.0, 2703.1, 2668.0, 2637.2, 2602.2, 2577.0, 2526.8, 2487.6, 1604.0, 1533.9, 1474.3, 1461.7, 1450.6, 1392.5, 1366.9, 1336.0, 1320.3, 1308.3, 1277.9, 1240.3, 1217.8, 1172.8, 1158.2, 911.7, 903.9, 893.3, 862.1, 845.4, 823.0, 797.0, 580.7, 560.0, 529.2, 512.2, 424.4 cm^{-1}.
MS: CI ($M+H^+$) m/z=229.2.
HRMS (m/z) 229.1356, calculated for $C_{14}H_{17}N_2O$, 229.1341.
^{1}H NMR (CD_3OD) δ 7.76 (1H, d, J=0.8 Hz), 7.59-7.53 (2H, m), 4.53 (1H, d, J=3.3 Hz), 4.33 (1H, d, J=3.7 Hz), 3.54 (1H, dd, J=9.3, 6.0 Hz), 2.58 (3H, s), 2.46 (1H, dd, J=13.4, 9.7 Hz), 2.18-1.87 (5H, m).
^{13}C NMR (CD_3OD) δ 163.2,156.7, 138.4, 131.4,123.7, 120.0, 111.0, 64.8, 60.5, 45.9, 38.1, 28.8, 26.9.

EXAMPLE 48

6-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-3-METHYL-BENZO[D]ISOXAZOLE, HCL SALT

[0103]

MP: decomposes 278°C.
IR: (KBr) 2990.9, 2954.3, 2925.9, 2879.8, 2859.4, 2825.1, 2714.4, 2690.8, 2652.3, 2548.8, 1619.0, 1611.7, 1602.1, 1464.0, 1450.7, 1435.5, 1415.7, 1393.9, 1372.4, 1365.6, 1353.5, 1327.6, 1309.8, 1266.4, 1165.0, 980.1, 939.1,

886.6, 855.4, 818.5, 798.3, 765.2, 675.2, 636.9, 438.4 cm-1.
MS: CI (M+H+) 229.2.
HRMS (m/z) 229.1346, calculated for $C_{14}H_{16}N_2O$, 229.1341.
^1H NMR (CD_3OD) δ 7.76 (1H, d, J=8.3 Hz), 7.60 (1H, d, J=0.6 Hz), 7.31 (1H, dd, J=8.3, 1.2 Hz), 4.58 (1H, d, J=2.9 Hz), 4.31 (1H, d, J=4.2 Hz), 3.58 (1H, dd, J=9.5, 6.0 Hz), 2.54 (3H, s), 2.48 (1H, dd, J=13.4, 9.6 hz), 2.14-1.87 (5H, m).
^{13}C NMR (CD_3OD) δ 164.7, 156.5, 145.9, 124.5, 123.2, 122.2, 108.3, 64.4, 60.5, 46.3, 38.1, 28.8, 26.9.

EXAMPLE 49

6-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-1,4-DIHYDRO-QUINOXALINE-2,3-DIONE, HCL SALT

[0104]

IR: (KBr) 3092.8, 3030.9, 2992.6, 2962.4, 2928.9, 2835.4, 2761.2, 2693.9, 2653.7, 1685.6, 1626.3, 1600.4, 1530.5, 1456.6, 1395.8, 1356.9, 1340.2, 1316.7, 1264.6, 894.3, 868.7, 851.6, 823.3, 769.8, 750.0, 742.8, 723.7, 686.5, 677.1, 647.6, 609.4, 583.9, 531.1, 470.3 cm^{-1}.
MS: CI (M+H+) m/z=258.2.
HRMS (m/z) 258.1250, calculated for $C_{14}H_{16}N_3O_2$, 258.1242.
^1H NMR (D_2O) δ 6.75 (1H, d, J=8.5 Hz), 6.63 (1H, d, J=8.5 Hz), 6.50 (1H, s), 4.30 (1H, d, J=3.5 hz), 4.19 (1H, s), 3.03 (1H, ap. t.), 2.15 (1H, dd, J=13.2, 9.9 Hz), 1.93-1.67 (5H, m).
^{13}C NMR (D_2O) δ 158.5, 158.1, 140.9, 126.8, 126.3, 125.5, 119.1, 116.4, 65.9, 62.2, 46.5, 37.9, 30.0, 28.6.

EXAMPLE 50

6-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-QUINOXALINE, HCL SALT

[0105]

MP: decomposes 240°C.
IR: (KBr) 3033.9, 2989.6, 2958.0, 2920.1, 2888.1, 2847.3, 2822.4, 2715.1, 2686.6, 2648.7, 2626.6, 2546.7, 2518.7, 1621.2, 1609.8, 1497.0, 1462.3, 1450.1, 1368.8, 1350.0, 1335.3, 1326.2, 1304.2, 1181.9, 1133.1, 1031.5, 980.6, 952.6, 901.5, 889.7, 870.9, 827.2, 524.2, 408.4 cm^{-1}.
MS: CI (M+H+) m/z=226.3.
^1H NMR (CD_3OD) δ 8.89 (2H, d, J=11.1, 1.9 Hz), 8.11 (1H, d, J=8.8 Hz), 8.05 (1H, s), 7.82 (1H, dd, J=8.8, 2.1 Hz), 4.71 (1H, d, J=4.1 Hz), 4.37 (1H, t, J=4.4 Hz), 3.68 (1H, dd, J=9.5, 6.1 Hz), 2.55 (1H, dd, J=13.4, 9.7 Hz), 2.26-1.90 (5H, m).

EXAMPLE 51

1-[4-(7-AZA-BICYCLO[2.2.1]HEPT-2-YL)-2-FLUORO-PHENYL]-ETHANONE, HCL SALT

[0106]

MP 180-183°C.
IR: (KBr) 3023.1, 2996.2, 2959.6, 2841.7, 2814.2, 2698.2, 2646.9, 2626.8, 2572.0, 2531.8, 2512.8, 1679.0, 1621.2, 1611.7, 1605.3, 1569.7, 1499.4, 1453.4, 1429.4, 1422.2, 1370.4, 1346.9, 1304.2, 1292.0, 1283.9, 1260.2, 1243.8, 1223.2, 1170.4, 1163.0, 1150.5, 1142.3, 1055.5, 965.0, 894.0, 878.5, 839.3, 775.3, 542.3, 523.9 cm-1.
MS: CI (M+H+) m/z=234.2.
^1H NMR (CD_3OD) δ 7.86-7.82 (1H, m), 7.25-7.22 (2H, m), 4.54 (1H, d, J=3.6 Hz), 4.31 (1H, t, J=4.2 Hz), 3.46 (1H, dd, J=9.4, 6.0 Hz), 2.58 (3H, dd, J=4.5, 0.8 Hz), 2.44 (1H, dd, J=13.5, 9.6 Hz), 2.11-1.85 (5H, m).
^{13}C NMR (CD_3OD) δ 163.8, 161.0, 149.53, 149.46, 130.70, 130.67, 122.81, 122.78, 114.99, 114.73, 62.5, 59.0, 44.4, 36.2, 29.8, 27.3, 25.4.

PREPARATION 1

7-CARBOETHOXY-2-CARBOXY-7-AZABICYCLO[2.2.1]-HEPTANE

[0107] A 1L round bottomed flask (RBF) was charged with 7-carboethoxy-2carboethoxy-7-azabicyclo[2.2.1]-heptane (28 g, 0.123 mol) and 250 mL THF.LiOH (8.8 g, 0.37 mol) was added in 86 mL H_2O and the walls of the flask were rinsed with methanol (MeOH) (86 mL). The reaction was stirred at room temperature for 4 hours. The reaction mixture was partitioned between 1L ethyl acetate (EtOAc) and 200 mL H_2O. The organics were separated and extracted with 1N sodium hydroxide (NaOH) (5 x 200mL). The combined aqueous phases were reacidified with 6N HCl (ca. 62 mL), extracted with EtOAc (5 x 200mL), dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to an oil. The oil was dried under vacuum to afford the title product which was used without purification for the next step (24 g, 0.34 mol, 92%).

MS: CI (m/z) 214 ($M+H^+$), 200 (60%), 186 (66%), 168 (87%).
^1H NMR (CD_3OD) δ 4.45 (1H, m), 4.30 (1H, m) 4.15 (2H, q, J=7 Hz), 2.55 (1H, m), 1.75 (2H, m), 1.55 (1H, m), 1.44 (1H, br, s), 1.20 (3H, dd).

PREPARATION 2

7-CARBOETHOXY-7-AZABICYCLO[2.2.1]-HEPTENE

[0108] A 1L RBF was charged with 7-carboethoxy-2-carboxy-7-azabicyclo[2.2.1]-heptane (14.7 g, 68.9 mol) in 750 mL benzene. After purging with N_2, solid copper acetate (2.5 g, 13.8mol) was added (a blue hue emerged) followed by lead tetraacetate (39.7 g, 89.6mol). The reaction was stirred wrapped in aluminum foil overnight under N_2 overnight and then brought to reflux for 2 hours. The reaction mixture was filtered through paper paper, and the solid brown residue was rinsed with 1.1 hexane/ether (4 × 100mL). The blue filtrate was again filtered and the concentrated residue was then passed through a plug (with 1:1 hexane/ether) to afford 4.6 g pure title compound and 4.3 slightly impure title compound (total 8.9 g, 53.2 mol, 77% yield).

MS: CI (m/z) 153 ($M+H^+$).
^1H NMR ($CDCl_3$) δ 6.21 (2H, br,s), 4.71 (2H, br, s,) 4.05 (2H, q, J=7 Hz), 1.84 (2H, d, J=11 Hz), 1.19 (3H, dd, J=7.2,1Hz), 1.10 (2H, d, J=1 Hz).

PREPARATION 3

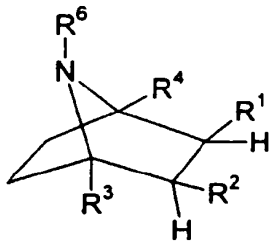
7-CARBO-*tert*-BUTOXY-7-AZABICYCLO[2.2.1]-HEPTENE

[0109] A 2-necked RBF equiped with a water-cooled condenser was flame-dried and charged with N_2 and a solution of 7-carboethoxy-7-azabicyclo[2.2.1]-heptene (1.0g, 6.01 mmol) in 10 mL $CHCl_3$. Triethylamine (TEA, 3.1 equiv., 2.59 ml) was added, followed by trimethylsilyl iodide (TMSI) (3.61g, 18 mmol, 3.0 equivalent (equiv.)), which was added dropwise, and the reaction was refluxed for 2 hours as the reaction color turned dark red. After cooling to room temperature, trifluoroacetic acid (TFA, 2.19 g, 1.48 mL, 19.2 mmol, 3.2 equiv.) was added and the reaction mixture was stirred at room temperature for 2 hours. After another addition of TEA (3.5 equiv.), t-butyl pyrocarbonate (2.61 g, 12.02 mmol) was added in 3.5 mL methylene chloride ($CHCl_3$), and the reaction was stirred overnight at room temperature. The reaction was worked up by partioning of the crude between 70 mL EtOAc and 30 mL water. The organics were separated of and washed with water (1 x 30 mL), dried (Na_2SO_4), filtered (paper), and concentrated *in vacuo* to afford a yellow solid. Flash chromatography (30g silicon dioxide (SiO_2), 90:10 hexane: ethyl acetate (EtOAc)) afforded the title product (0.850 g, 72%).

MS: CI (m/z) 181 ($M+H^+$).
^1H NMR ($CDCl_3$) δ 6.20 (2H, br,s), 4.64 (2H, br, s,) 1.83 (2H, br, s), 1.83 (2H, d, J=8.7 Hz), 1.45 (9H, s), 1.08 (2H, d, J=1 Hz).

Claims

1. A compound of the formula



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wherein

R^1, R^2, R^3 and R^4 are selected, independently from hydrogen, $-CO_2R^5$, aryl and heteroaryl, wherein said aryl is selected from phenyl and naphthyl and said heteroaryl is selected from pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, 1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolinyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl oxazolyl, isoxazoyl, thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl, pyridinyl, and pyrimidinyl, and wherein said phenyl and said heteroaryl may optionally be substituted with from one to three substitutuents, and are preferably substituted with one or two substutituents, independently selected form $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, halo (i.e., chloro, fluoro, bromo or iodo), phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, $(C_1\text{-}C_6)$alkoxy optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, $(C_1\text{-}C_6)$alkylamino and $[(C_1\text{-}C_6)\text{alkyl}]_2$amino;
R^5 is $(C_1\text{-}C_6)$ alkyl, aryl, heteroaryl, $(C_1\text{-}C_4)$alkylene-aryl and $(C_1\text{-}C4)$alkylene-heteroaryl, wherein said aryl and heteroaryl are defined as above, and wherein said $(C_1\text{-}C_6)$alkyl may optionally be substituted with from one to three substituents independently selected from halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6$)alkoxy, $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl, amino, $(C_1\text{-}C_6)$alkylamino, and $[(C_1\text{-}C_6)\text{alkyl}]_2$amino; and
R^6 is hydrogen or $(C_1\text{-}C_6)$alkyl;

with the proviso that: (a) at least one of R^1, R^2, R^3, and R^4 must be aryl or heteraryl; (b) when neither R^1 nor R^2 is hydrogen, R^1 and R^2 are in the "exo" configuration; (c) R^1 and R^2 can not both be $-CO_2R^5$; (d) if either R^3 or R^4 is CO_2R^5 and R^5 is an alkyl or alkoxyalkyl group, then one of R^1 and R^2 must be aryl or heteroaryl; and (e) if either R^1 or R^2 is CO_2R^5 and R^5 is an alkyl or alkoxyalkyl group, then one of R^3 and R^4 must be aryl or heteroaryl;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^3 and R^4 are hydrogen, and one of R^1 and R^2 is optionally substituted phenyl and the other is hydrogen.

3. A compound according to claim 1, wherein R^3 and R^4 are hydrogen, and one of R^1 and R^2 is phenyl substituted with fluoro or nitro and the other is hydrogen.

4. A compound according to claim 1, wherein R^3 and R^4 are hydrogen and one of R^1 and R^2 is hydrogen and the other is: (a) 3-fluorophenyl; (b) 4-nitrophenyl; or 3-fluoro-4-nitrophenyl.

5. A pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

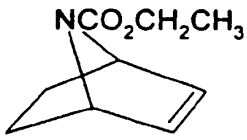
6. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

7. A pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion,

ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, headache, stroke, TBI, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

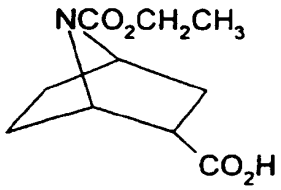
8. A method for treating a disorder or condition selected from inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, headache, stroke, TBI, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound according to claim 1 that is effective in treating such disorder or condition.

9. A process for preparing a compound of the formula



XVI

comprising reacting a compound of the formula



XVII

with lead tetraacetate and copper acetate.

10. A process according to claim 9 which is conducted at the reflux temperature using benzene, toluene or xylenes as the solvent.

11. A process according to claim 10 which is conducted using benzene as the solvent.

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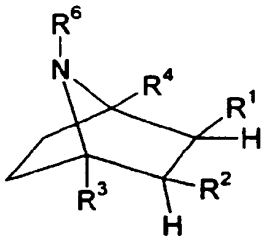
(54) 7-aza-bicyclo[2.2.1]-heptane derivatives, their preparation and use according to their affinity for neuronal nicotinic acetylcholine receptors

(57) Compounds of the formula



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wherein R^1, R^2, R^3 and R^4 are selected, independently from hydrogen, $-CO_2R^5$, aryl and heteroaryl, wherein said aryl is selected from phenyl and naphthyl and said heteroaryl is selected from pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, 1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolinyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolyl, isoxazoyl, thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl, pyridinyl, and pyrimidinyl, and wherein said phenyl and said heteroaryl may optionally be substituted with from one to three substituents, and are preferably substituted with one or two substituents, independently selected form $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms, halo, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, $(C_1\text{-}C_6)$alkoxy optionally substituted with from one to seven fluorine atoms, $(C_1\text{-}C_6)$alkylamino and $[(C_1\text{-}C_6)\text{alkyl}]_2$amino;

R^6 is hydrogen or $(C_1\text{-}C_6)$alkyl;

with the proviso that: (a) at least one of R^1, R^2, R^3, and R^4 must be aryl or heteroaryl; (b) when neither R^1 nor R^2 is hydrogen, R^1 and R^2 are in the "exo" configuration; (c) R^1 and R^2 can not both be $-CO_2R^5$; (d) if either R^3 or R^4 is CO_2R^5 and R^5 is an alkyl or alkoxyalkyl group, then one of R^1 and R^2 must be aryl or heteroaryl; and (e) if either R^1 or R^2 is CO_2R^5 and R^5 is an alkyl or alkoxyalkyl group, then one of R^3 and R^4 must be aryl or heteroaryl;

and their pharmaceutically acceptable salts, pharmaceutical compositions containing such compounds and methods of using such compounds in the treatment of neurological and psychological disorders.

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which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO 93 18037 A (THE UNITED STATES OF AMERICA, DEPT. OF HEALTH AND HUMAN SERVICES) 16 September 1993 (1993-09-16) * claims 2,5,7 *	1-4,7,8	C07D487/08 A61K31/40 A61K31/44 A61K31/41 A61K31/505 //(C07D487/08, 209:00,209:00)
D,X	WO 94 22868 A (UNIVERSITY OF VIRGINIA) 13 October 1994 (1994-10-13) * claims 1-9,14-27,42-46; examples 25,40,44,54-56,60,63,64 *	1-3,7,8	
D,X	WO 95 07078 A (CYTOMED INC. & UNIVERSITY OF VIRGINIA) 16 March 1995 (1995-03-16) * claims 1-3,7-9,12-14; table I *	1-8	
D,X	EP 0 657 455 A (EGIS GYOGYSZERGYAR) 14 June 1995 (1995-06-14) * claims 1-5,15,16; examples 12,19,26,33,42,48 *	1-4,7,8	
D,X	EP 0 664 293 A (DUPHAR INTERNATIONAL RESEARCH B.V.) 26 July 1995 (1995-07-26) * page 2, line 25 - line 26; claims 1-4; example I *	1-4,7,8	

-/--

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	22 February 2001	Hartrampf, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 99 30 2306

Although claims 6 and 8 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:
2-5,7,9-11

Claim(s) searched incompletely:
1

Reason for the limitation of the search:

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty (for the first invention), see also the "Background of the Invention" part on pages 1/2 of the application. So many relevant documents were cited and/or retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 84 EPC). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search (for the first invention) has been restricted to the compounds of formula (I) wherein one of R1 and R2 is optionally substituted phenyl, i.e. most of the compounds exemplified and covered by claims 2-4.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 99 30 2306

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CHEMICAL ABSTRACTS, vol. 123, no. 11, 11 September 1995 (1995-09-11) Columbus, Ohio, US; abstract no. 132835k, AKASAKA, K. ET AL.: "Preparation of azabicycloheptane derivatives and their use as pharmaceuticals including analgesics" page 130; column 1; XP002149521 * abstract *	1-4,7,8	
D	& JP 07 061940 A (EISAI CO., LTD.) 7 March 1995 (1995-03-07) * column 12 - column 13 * * column 16 * * column 18 - column 22 *		TECHNICAL FIELDS SEARCHED (Int.Cl.6)
D,X	WO 96 06093 A (UNIVERSITY OF VIRGINIA) 29 February 1996 (1996-02-29) * claims 1-3,5-7,14-25,27-30,32-34; figures 3,4,6; examples 25,40,44,54-56,60,81,82,84-90,93-95 *	1-3,7,8	
P,X	WO 98 46609 A (ABBOTT LABORATORIES) 22 October 1998 (1998-10-22) * claims 1-8,13,14 *	1,5,7	
D,X	WO 95 03306 A (E.I. DU PONT DE NEMOURS AND COMPANY) 2 February 1995 (1995-02-02) * claims 1,5,10 *	1	
	-/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 99 30 2306

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	HUISGEN R. ET AL.: "1-Pyrrolines and 7-azabicyclo[2.2.1]heptane from azlactones and activated alkenes" CHEMISCHE BERICHTE, VERLAG CHEMIE GMBH. WEINHEIM, DE, vol. 103, no. 8, 1970, pages 2368-2387, XP000984022 * compounds 17, 19, 24, 26, 40 * ---	1	
A	MARCHAND A.P. & ALLEN R.W.: "Synthesis of 7-azanorbornene and N-methyl-7-azanorbornene" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US , vol. 40, no. 17, 1975, pages 2551-2552, XP000941118 * scheme I, compound 8 * -----	9-11	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

EPO FORM 1503 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 30 2306

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22-02-2001

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

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(81) Etats désignés: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, brevet ARIPO (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Publiée
Avec rapport de recherche internationale.

(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING NICOTINE OR A LIGAND OF NICOTINE RECEPTORS AND A MONAMINE OXYDASE INHIBITOR AND THEIR USE FOR TREATING TOBACCO WITHDRAWAL SYMPTOMS

(54) Titre: COMPOSITIONS PHARMACEUTIQUES CONTENANT DE LA NICOTINE OU UN LIGAND DES RECEPTEURS NICOTINIQUES ET UN INHIBITEUR DE LA MONAMINE OXYDASE ET LEUR APPLICATION DANS LE SEVRAGE TABAGIQUE

(57) Abstract

The invention concerns novel pharmaceutical compositions containing nicotine or a ligand of nicotine receptors and a monamine oxydase inhibitor designed for treating tobacco withdrawal symptoms.

(57) Abrégé

Nouvelles compositions pharmaceutiques comprenant de la nicotine ou un ligand des récepteurs nicotiniques ainsi qu'un inhibiteur de la monoamine oxydase, destinées au sevrage tabagique.

UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

AL	Albanie	ES	Espagne	LS	Lesotho	SI	Slovénie
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COMPOSITIONS PHARMACEUTIQUES CONTENANT DE LA NICOTINE OU UN LIGAND DES RECEPTEURS NICOTINIQUES ET UN INHIBITEUR DE LA MONAMINE OXYDASE ET LEUR APPLICATION DANS LE SEVRAGE TABAGIQUE

La présente invention a pour objet une nouvelle composition pharmaceutique comprenant de la nicotine ou un ligand des récepteurs nicotinique destinée au sevrage tabagique.

La consommation de tabac est considérée comme un vrai problème de santé publique, dans la mesure où le tabac est à l'origine de plusieurs maladies graves telles que les maladies cardio-vasculaires, respiratoires et certains types de cancer. L'administration de la nicotine ou d'un analogue tel que la lobéline par voie transdermique ou au moyen de gomme à macher ou spray nasal par exemple, constitue un traitement de substitution à la consommation de tabac et par conséquent un outil de sevrage tabagique. Cependant, la prise de ce type de médication n'est pas dénuée d'effets indésirables, en particulier, une élévation de la pression artérielle, de la fréquence cardiaque et des effets gastro-intestinaux. D'ailleurs, les composés disponibles sur le marché comme (Nikoban®, Bantron®, CigArrest® et Nic-Fit®) par exemple sont souvent administrés avec des antiacides pour éviter les effets gastro-intestinaux indésirables.

La nicotine, comme d'autres substances d'origines diverses (alcool, cocaïne...), provoque une dépendance. Ces molécules agissent via des mécanismes primaires distincts conduisant à l'activation d'un mécanisme commun responsable du plaisir induit par leur consommation. Parmi les neurotransmetteurs du système nerveux central impliqués dans les phénomènes de dépendances, la dopamine joue un rôle majeur lié à son implication dans les comportements hédoniques.
Les inhibiteurs de la monoamine oxydase (IMAO) - la monoamine oxydase étant un flavoenzyme impliqué dans le catabolisme des amines biogènes dont la dopamine - ont été

décrits comme potentiellement bénéfiques dans le traitement du sevrage tabagique (I. Berlin *et coll., Clin. Pharmacol. Ther* (1995), **58**(4), 444-452).

Il est également connu par exemple, que les IMAO de type B sont potentiellement utiles dans ce type de traitement (voir Fowler et coll., Neuropharmacological actions of cigarette smoke : brain monoamine oxydase B (MAOB) inhibition. *J.add.disease* (1998), **17**, 23-34 et Fowler et coll. Nature (1996), **379**, 733-736).

De même, dans la demande de brevet WO95/28934, l'utilisation des inhibiteurs de la monoamine oxydase A pour le contrôle de la consommation tabagique, et en particulier lors des états de manque, est décrite. En augmentant la quantité de dopamine au niveau des centres du plaisir localisés dans le système limbique, ces composés pourraient en reproduire la sensation hédonique associée au tabagisme et favoriser le sevrage tabagique.

Le brevet US 5,803,081 évoque la possibilité de réaliser une gomme à mâcher (chewing gum) contenant du tabac coupé traité au propolis, à titre de réservoir pour une libération prolongée de nicotine, et éventuellement d'un inhibiteur de monoamine oxydase B tel que trouvé dans la fumée du tabac. Les avantages cités pour cette gommme à mâcher réside dans le prétraitement du tabac par le propolis, permettant d'éviter des pics de libération de la nicotine tout en prolongeant la saveur de la gomme à mâcher. Toutefois, non seulement, la présence d'inhibiteur de la monoamine oxydase B n'y est pas décrite comme indispensable pour atteindre les avantages précités, mais encore aucun inhibiteur de la monoamine oxydase B n'est spécifiquement cité dans sa structure ni même dans son éventuel rôle dans cette gomme à mâcher. Par ailleurs, la gomme à mâcher elle-même n'est pas illustrée par un exemple de réalisation technique.

Le but de la présente invention est de fournir une composition pharmaceutique comprenant de la nicotine ou un ligand des récepteurs nicotiniques, utile dans le sevrage tabagique et dont les effets secondaires cardio-vasculaires

sont réduits.

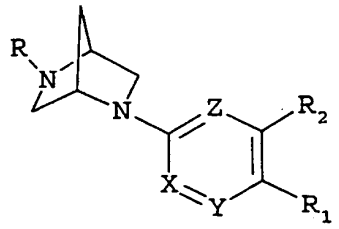
La demanderesse a en effet pu mettre en évidence, de façon surprenante, que les effets secondaires subséquents à l'administration de nicotine ou un ligand des récepteurs nicotiniques peuvent être considérablement réduits grâce à la co-administration d'un inhibiteur de la monoamine oxydase.

L'invention a donc pour objet une composition pharmaceutique comprenant de la nicotine ou un ligand des récepteurs nicotiniques et un inhibiteur de la monoamine oxydase, utile pour le sevrage tabagique et dont les effets secondaires cardio-vasculaires sont réduits.

On entend par ligand des récepteurs nicotinique, dans le cadre de la présente invention, notamment les agonistes des récepteurs nicotiniques tels que la cytisine, la lobéline, l'ABT-418 (Abbott), l'épibatidine, le GTS-21, le AR-R17779 (AstraZeneca), le ABT-594 (Abbott), le ABT-089 (Abbott), mais aussi d'autres ligands des récepteurs nicotiniques tels que :
le AN-072 (Elan), l'eperisone (Eisai), le bromure de rapacuronium (Akzo Nobel), l'altinicline (Sibia), le conantokin-G (Cognetix), le GW-280430 (Glaxo Wellcome), le RJR-2403 (Targacept), la galantamine, le SIB 1553 A (Sibia), le A-85380 (Abbott), la métanicotine, le RJR-2531 (R.J. Reynolds Tobacco), le RJR-2557 (R.J. Reynolds Tobacco), le DBO-83 (universités de Florence et Milan), la 9-bromo-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one (Pfizer), la 11-fluoro-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one (Pfizer), la 9-phényl-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one (Pfizer), la 9-benzyl-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one (Pfizer), la 9-acétyl-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one (Pfizer), la 9-(2-pyridyl)-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one (Pfizer),

9-(2,4-difluorophényl)-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one (Pfizer), la 9-(2-thiazolyl)-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one (Pfizer), l'endo-6-(3-pyridyl)-2-azabicyclo[2.2.2]octane (Sumitomo Pharmaceuticals), l'endo-6-(5-pyrimidinyl)-2-azabicyclo[2.2.2]octane (Sumitomo Pharmaceuticals), le 6-(5-bromo-3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ène (Sumitomo Pharmaceuticals), le 6-(5-éthynyl-3-pyridyl)-2-azabicyclo[2.2.2]octane (Sumitomo Pharmaceuticals), le (±)-8-méthyl-3-(3-pyridyl)-8-azabicyclo[3.2.1]oct-2-ene (Neurosearch), le (±)-8-(benzyl)-3-(3-pyridyl)-8-azabicyclo[3.2.1]oct-2-ène (Neurosearch), le (±)-3-(6-chloro-3-pyridinyl)-8-méthyl-8-azabicyclo[3.2.1]oct-2-ene (Neurosearch), le (±)-3-(8-méthyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)aniline (Neurosearch), la spiro[1,3-benzodioxole-2,3'-quinuclidine] (Neurosearch), la 5-méthylspiro[1,3-benzodioxole-2,3'-quinuclidine] (Neurosearch), la 5-tert-butylspiro[1,3-benzodioxole-2,3'-quinuclidine] (Neurosearch), la (±)-3-(5-méthoxy-3-pyridinyl)-9-azabicyclo[3.3.1]non-2-ène (Neurosearch), la (±)-3-(5-méthoxy-3-pyridinyl)-9-méthyl-9-azabicyclo[3.3.1]non-2-ène (Neurosearch), la (±)-3-(9-méthyl-9-azabicyclo[3.3.1]non-2-èn-3-yl)phénylamine (Neurosearch), le (±)-3-(3-pyridinyl)-9-azabicyclo[3.3.1]non-2-ène (Neurosearch), la (±)-9-méthyl-3-(3-pyridinyl)-9-azabicyclo[3.3.1]non-2-ène (Neurosearch), le spiro[1-azabicyclo[2.2.2]octane-3-2'(3'H)-furo[2,3-b]pyridine]7'-oxide (AstraZeneca), la 1-(6-chloro-5-méthoxypyridin-3-yl)perhydro-1,4-diazépine (Neurosearch), la 1-(5-méthoxypyridine-3-yl)perhydro-1,4-diazépine (Neurosearch), la 1-(5-méthoxypyridin-3-yl)perhydro-1,5-diazocine (Neurosearch), la 3-(perhydro-1,4-diazépin-1-yl)quinoline (Neurosearch), la 1-(6-bromopyridin-3-yl)perhydro-1,4-diazépine (Neurosearch), la 1-(5-propoxypyridin-3-yl)perhydro-1,4-diazépine (Neurosearch), la 4-(3-pyridinyloxy)perhydroazépine (Neurosearch), la 2-méthyl-1,2,3,5,6,7,8,9-octahydro-5,9-méthanopyrrolo

[3,4-h][3]benzazépine-1,3-dione (Pfizer), la 1,3-diméthyl-1,2,3,5,6,7,8,9-octahydro-5,9-méthanoimidazo [4,5-h][3]benzazépin-2-one (Pfizer), la 1,2,3,5,6,7,8,9-octahydro-5,9-méthanopyrrolo[3,4-h][3] benzazépine-1,3-dione (Pfizer), la 7,8-difluoro-2,3,4,5-tétrahydro-1H-1,5-méthano-3-benzazépine (Pfizer), le 8-éthynyl-2,3,4,5-tétrahydro-1H-1,5-méthano-3-benzazépine-7-carbonitrile (Pfizer), la 7-chloro-8-(trifluorométhyl)-2,3,4,5-tétrahydro-1H-1,5-méthano-3-benzazépine (Pfizer), le 8-(trifluorométhyl)-2,3,4,5-tétrahydro-1H-1,5-méthano-3-benzazépine-7-carbonitrile (Pfizer),
ainsi que ceux décrits :
- dans la demande de brevet WO98/42713, c'est à dire les dérivés de 2,3-dihydrofuro[3,2-b]pyridine et plus particulièrement les composés (*R*,*R*),(*S*,*S*),(*R*,*S*) et (*S*,*R*) de la 2-pyrrolidin-2-yl-2,3-dihydrofuro[3,2-*b*]pyridine et,
- dans la demande de brevet WO99/02517, c'est à dire les dérivés de 6,7-dihydro-5*H*-2-pyrindine et plus particulièrement les composés (*R*,*R*),(*S*,*S*), (*R*,*S*) et (*S*,*R*) de la 6-pyrrolidin-2-yl-6,7-dihydro-5*H*-2-pyridine
- les composés décrits dans la demande de brevet PCT/FR99/02974 utiles dans le traitement ou la prévention des désordres liés à un dysfonctionnement des récépteurs nicotiniques, notamment au niveau du système nerveux central ou du système gastrointestinal (par exemple les altérations cognitives, schizophrénie, dépression, douleur...), répondant à la formule générale (I)



(I)

dans laquelle
l'un des symboles X, Y et Z représente un atome d'azote, un autre représente un groupe de formule C-R_3 et le troisième représente un atome d'azote ou un groupe de formule C-R_4,

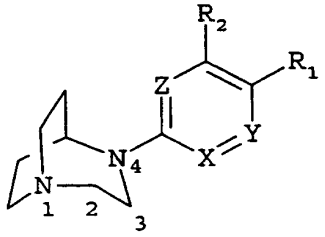
R_3 et R_4 représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou d'halogène ou un groupe trifluorométhyle, cyano, hydroxy, (C_1-C_6)alkyle ou (C_1-C_6)alcoxy,

R_1 et R_2 représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou d'halogène ou un groupe trifluorométhyle, cyano, hydroxy, (C_1-C_6)alkyle, (C_1-C_6)-alcoxy, ou phényle éventuellement substitué par un ou deux atomes d'halogènes, par un ou deux groupes trifluoro-méthyle, par un groupe cyano, par un groupe nitro, par un groupe hydroxy, par un groupe (C_1-C_6)alkyle, par un ou deux groupes (C_1-C_6)alcoxy, par un groupe méthylènedioxy, par un groupe acétyle, par un groupe trifluorométhoxy ou par un groupe méthylthio,

R représente un atome d'hydrogène ou un groupe (C_1-C_6)alkyle,

étant toutefois exclus les composés de formule générale (I) dans laquelle X représente un groupe de formule CH, Y et Z représentent chacun un atome d'azote, et R_1 ou R_2 ne représente pas un groupe phényle éventuellement substitué,

- les composés décrits dans la demande de brevet PCT/FR99/02975, également utiles dans le traitement ou la prévention des désordres liés à un dysfonctionnement des récépteurs nicotiniques, notamment au niveau du système nerveux central ou du système gastrointestinal, répondant à la formule générale (I)



(I)

dans laquelle

l'un des symboles X, Y et Z représente un atome d'azote, un autre représente un groupe de formule C-R_3 et le troisième représente un atome d'azote ou un groupe de formule C-R_4,

R_3 et R_4 représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou d'halogène ou un groupe trifluorométhyle, cyano, hydroxy, (C_1-C_6)alkyle ou (C_1-C_6)alcoxy,

R_1 et R_2 représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou d'halogène ou un groupe trifluorométhyle, cyano, hydroxy, (C_1-C_6)alkyle, (C_1-C_6)alcoxy, ou phényle éventuellement substitué par un atome d'halogène, par un ou deux groupes trifluorométhyle, par un groupe cyano, par un groupe nitro, par un groupe hydroxy, par un groupe (C_1-C_6)alkyle, par un groupe (C_1-C_6)alcoxy, par un groupe acétyle, par un groupe méthylènedioxy, par un groupe trifluorométhoxy, par un groupe méthylthio ou par un groupe phényle.

Parmi les ligands des récepteurs nicotiniques, on préfère les agonistes.

Grâce à la composition selon la présente invention, l'augmentation de la pression artérielle et de la fréquence cardiaque est minimisée. La composition assure une plus grande sécurité et une meilleure tolérance et donc une meilleure compliance du traitement pour le patient.

Par ailleurs, l'association d'un inhibiteur de la monoamine oxydase A réversible ou A,B mixte réversible ou bien B réversible ou irréversible, avec la nicotine ou un ligand des récepteurs nicotiniques peut avoir un effet amplificateur des effets bénéfiques de la nicotine par exemple la sensation de plaisir, l'amélioration de l'humeur, l'amélioration des performances psychomotrices et cognitives tout en réduisant les effets secondaires, notamment cardio-vasculaires.

Dans le cadre de la présente invention, on préfère les compositions comprenant la nicotine ou un ligand des récepteurs nicotiniques et un inhibiteur réversible de la monoamine oxydase.

Dans le cadre de la présente invention, l'inhibiteur de la monoamine oxydase peut être un inhibiteur de la monoamine oxydase A réversible, un inhibiteur de la monoamine oxydase B réversible ou irréversible ou un inhibiteur de la

monoamine oxydase A,B mixte réversible.
Plus particulièrement à titre d'IMAO A réversible on peut citer : la béfloxatone, le moclobémide, la brofaromine, la phénoxathine, l'esuprone, le befol, le RS 8359 (Sankyo), le T794 (Tanabé), le KP 9 (Krenitsky, USA), le E 2011 (Eisai), la toloxatone, le pirlindole, l'amiflamine, la sercloremine, la bazinaprine,
A titre d'IMAO B réversible on peut citer : le lazabemide, le milacémide, la caroxazone, l'IFO,
A titre d'IMAO B irréversible on peut citer : le L-deprényl, la mofégiline, la rasagéline, la pargyline.

A titre d'IMAO on peut encore citer les composés décrits :
- dans la demande de brevet WO96/38444, c'est à dire des dérivés d'oxazolidin-2-one et par exemple la (*S*)-5-méthoxyméthyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one,
- dans la demande de brevet EP 0 699 680, c'est à dire des dérivés de 3,3*a*,4,5-tétrahydro-1*H*-oxazolo[3,4-*a*]quinoléin-1-one et par exemple la [3(*S*),3*a*(*S*)]-3-méthoxyméthyl-7-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)-3,3*a*,4,5-tétrahydro-1*H*-oxazolo[3,4-*a*]quinoléin-1-one et la [3(*S*),3*a*(*S*)]-3-méthoxyméthyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tétrahydro-1*H*-oxazolo[3,4-a]quinoléine-1-one,
- dans la demande de brevet WO97/13768, c'est à dire des dérivés d'oxazolidin-2-one et par exemple la (*R*)-5-(méthoxyméthyl)-3-[6-(4,4,4-trifluorobutoxy) benzofuran-3-yl]oxazolidin-2-one et la (*R*)-5-méthoxyméthyl-3-(6-cyclopropylméthoxybenzofuran-3-yl)oxazolidin-2-one,
- dans la demande de brevet WO97/17347, c'est à dire des composés dérivés d'oxazolidin-2-one et par exemple la (-)3-[2-(3,3,3-trifluoropropyl)-3,4-dihydro-2*H*-1-benzopyran-6-yl]-5(*R*)-méthoxyméthyloxazolidin-2-one et la 3-[2-(3,3,3-trifluoropropyl)-2,3-dihydrobenzofuran-5-yl]-5(*R*)-méthoxyméthyloxazolidin-2-one,
- dans la demande de brevet WO97/17346, c'est à dire des composés dérivés de 3-(benzofuran-5-yl)oxazolidin-2-one et par exemple la 3-[2-(3,3,3-trifluoropropyl)benzofuran-5-yl]-5(*S*)-méthoxyméthyloxazolidin-2-one, la

3-(2-propylbenzofuran-5-yl)-5(*R*)-méthoxyméthyloxazolidin-2-one et la 3-(2-phénylbenzofuran-5-yl)-5(*S*)-méthoxyméthyloxazolidin-2-one,

- dans la demande de brevet EP 0 655 445, c'est à dire des dérivés de 1,3,4-oxadiazol-2(3*H*)-one et par exemple la 5-[4-(4,4,4-trifluorobutoxy)phényl]-3-(2-méthoxyéthyl)-1,3,4-oxadiazol-2(3*H*)-one.

La béfloxatone et la moclobémide sont tout particulièrement préférés à titre d'inhibiteur de la monoamine oxydase A réversible ainsi que la (-)3-[2-(3,3,3-trifluoropropyl)-3,4-dihydro-2*H*-1-benzopyran-6-yl]-5(*R*)-méthoxyméthyloxazolidin-2-one.

La (*S*)-5-méthoxyméthyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one est tout particulièrement préféré à titre d'inhibiteur de la monoamine oxydase B réversible.

La [3(*S*),3*a*(*S*)]-3-méthoxyméthyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tétrahydro-1*H*-oxazolo[3,4-a]quinoléine-1-one est tout particulièrement préféré à titre d'inhibiteur de la monamine oxydase A,B mixte réversible, ainsi que la (*R*)-5-(méthoxyméthyl)-3-[6-(4,4,4-trifluorobutoxy) benzofuran-3-yl]oxazolidin-2-one et la (*R*)-5-méthoxyméthyl-3-(6-cyclopropylméthoxybenzofuran-3-yl)oxazolidin-2-one.

Parmi les différentes classes d'IMAO citées, on préférera, pour les compositions selon la présente invention, les IMAO A et A,B mixtes réversibles.

Un autre objet de la présente invention consiste en une composition pharmaceutique comprenant de la nicotine ou ligand des récepteurs nicotiniques et un inhibiteur de la monoamine oxydase comme produit de combinaison pour une utilisation simultanée, séparée ou étalée dans le temps destiné au sevrage tabagique.

On entend par "utilisation simultanée" l'administration des composés de la composition selon l'invention compris dans une seule et même forme pharmaceutique.

On entend par "utilisation séparée" l'administration, en même temps, des deux composés de la composition selon l'invention chacun compris dans une forme pharmaceutique distincte.

On entend par "utilisation étalée dans le temps" l'administration successive, du premier composé de la composition selon l'invention, compris dans une forme pharmaceutique, puis, du deuxième composé de la composition selon l'invention, compris dans une forme pharmaceutique distincte.

Dans le cas de cette "utilisation étalée dans le temps", le laps de temps écoulé entre l'administration du premier composé de la composition selon l'invention et l'administration du deuxième composé de la même composition selon l'invention n'excède généralement pas 24 heures.

Les formes pharmaceutiques, comprenant soit un seul des composés constitutifs de la composition selon l'invention soit l'association des deux composés, qui peuvent être mises en oeuvre dans les différents types d'utilisations décrites ci-dessus, peuvent par exemple être appropriées à l'administration orale, nasale, parentérale ou transdermique.

Aussi, dans le cas d'une "utilisation séparée" et d'une "utilisation étalée dans le temps", les deux formes pharmaceutiques distinctes peuvent être destinées à la même voie d'administration ou à une voie d'administration différente (orale et transdermique ou orale et nasale ou parentérale et transdermique etc).

Toutes ces formes pharmaceutiques font également partie de l'invention.

Parmi les formes pharmaceutiques adaptées à l'administration orale, on peut citer les comprimés, gélules, pilules et les gommes à mâcher à libération immédiate ou prolongée.

Pour l'administration parentérale, les formes galéniques telles que suspensions ou solutions injectables conviennent.
La composition selon l'invention peut alors être administrée en une dose journalière unique ou en doses journalières fractionnées. Dans ce dernier cas la composition peut être administrée en 2 à 3 prises par jour.

Les timbres transdermiques ou patchs sont par exemple adaptés pour l'administration transdermique. Pour l'administration locale, des gels ou émulsions sont également adaptés.
On préfère particulièrement le patch ou timbre transdermique qui permet une administration lente et régulière pour l'un au moins des deux composés de l'association. L'autonomie du patient vis-à-vis de son traitement est ainsi favorisée.
Le patch permet d'obtenir une libération de la composition qui peut durer entre 8 et 72 heures.

Les compositions pharmaceutiques appropriées à être mises en oeuvre dans un patch ou timbre transdermique peuvent se présenter sous forme de gel, de pommade, de solution, de crème ou d'émulsion. Elles peuvent être préparées selon les procédés conventionnels pour l'homme du métier.

Les compositions peuvent encore être formulées sous forme de spray nasal, spray pulmonaire ou suppositoire.

De manière préférée l'un au moins des deux composants de l'association est administrée par voie transdermique, par exemple par patch ou timbre transdermique. On pourra par exemple administrer l'IMAO par voie orale et la nicotine ou le ligand des récepteurs nicotiniques par patch ou bien l'inverse ou bien l'IMAO et la nicotine ou le ligand des récepteurs nicotiniques tous les deux par patch ou timbre transdermique.

Habituellement les compositions pharmaceutiques selon la

présente invention sont dosées pour permettre une administration journalière de 2 à 20 mg de nicotine ou de ligand des récepteurs nicotiniques et de 1 à 20 mg d'inhibiteur de la monoamine oxydase.

Enfin, la présente invention a aussi pour objet l'utilisation de nicotine ou un ligand des récepteurs nicotiniques et d'un inhibiteur de la monoamine oxydase pour la fabrication d'un médicament destiné au sevrage tabagique.

L'effet de l'association d'un inhibiteur de la monoamine oxydase à la nicotine sur la pression artérielle moyenne et sur la fréquence cardiaque a fait l'objet d'une étude qui a mis en évidence l'intérêt de cette association dans le sevrage tabagique.

MATERIEL ET METHODES

L'étude a été réalisée sur des rats mâles de souche Sprague-Dawley pesant de 277 à 345 g le jour du traitement.

On met en suspension dans un véhicule (Tween 80 0,5% w/v, méthylcellulose 0,5% w/v dans l'eau pour préparation injectable) de la béfloxatone ou du moclobémide.
On met en solution dans l'eau de la nicotine pour une préparation injectable.

Schéma expérimental

Les animaux ont subi, sous anesthésie générale par injection intrapéritonéale de kétamine (116 mg/kg i.p.), un cathétérisme de la carotide et de la veine jugulaire avec extériorisation des cathéters en région dorso-scapulaire. Le jour suivant l'implantation, les animaux ont été connectés à des appareils de mesure permettant l'enregistrement en continu de la pression artérielle et de la fréquence cardiaque.

Après une période de stabilisation de 30 minutes environ, les animaux ont reçu le traitement par voie orale, puis 45 minutes plus tard, trois doses croissantes de nicotine, administrées par voie intraveineuse à 5 minutes d'intervalle.
Les animaux ont ensuite été euthanasiés par injection intra-cardiaque de Doléthal.

Traitement

Deux groupes d'animaux ont été constitués (n=7/groupe). L'un a été traité avec la befloxatone à la dose de 1 mg/kg p.o., sous un volume de 5 ml/kg. L'autre groupe a reçu dans les mêmes conditions un volume équivalent de véhicule.
D'autre part, deux autres groupes d'animaux ont été constitués (n=6/groupe). L'un a été traité avec le moclobémide à la dose de 10 mg/kg p.o., soit un volume de 5 ml/kg. L'autre a reçu dans ces mêmes conditions un volume équivalent de véhicule.
Chaque animal a reçu la nicotine aux doses de 30, 50 et 100 µg/kg, successivement, sous forme de bolus intraveineux sur 30 secondes environ.

Paramètres mesurés

La pression artérielle moyenne et la fréquence cardiaque ont été mesurées avant traitement, avant chaque administration de nicotine, ainsi qu'à l'acmé de l'effet de ces administrations.

Expression des résultats

L'homogénéité des valeurs de base (pour la pression artérielle moyenne et la fréquence cardiaque) entre les groupes avant chaque administration (traitement ou nicotine) a été vérifiée par une analyse de variance à 2 facteurs (groupe x temps) avec mesures répétées sur le temps.

Les valeurs obtenues avant traitement, avant la première injection de nicotine et à l'acmé de l'effet de chaque dose de nicotine ont été relevées et présentées sous forme de moyennes ± ESM.

Les groupes traités avec la béfloxatone et le moclobémide ont été comparés aux groupes témoins respectifs par une analyse de variance à 2 facteurs (groupe x dose de nicotine) avec mesures répétées sur la dose de nicotine, suivie d'un test de Dunnett à niveau fixé de dose de nicotine.

RESULTATS ET CONCLUSIONS

Dans ces conditions expérimentales, la nicotine provoque chez les animaux témoins une élévation de la pression artérielle moyenne et une légère augmentation de la fréquence cardiaque.

La béfloxatone à 1 mg/kg p.o. et le moclobémide à 10 mg/kg p.o. réduisent les augmentations de pression artérielle et de fréquence cardiaque induites, entre 45 min et 60 min après le traitement, par des administrations intraveineuses de nicotine. (TAB.1 à 4).

TAB.1 : Pression artérielle moyenne (mm Hg), rat vigile

Traitement	avant traitement	avant nicotine	nicotine 30 µg/kg	nicotine 50 µg/kg	nicotine 100 µg/kg
véhicule (n=7)	101,1±2,1	100,4±2,9	122,3±5,3	123,1±5,6	132,9±6,2
Béfloxatone (n=7)	105,2±4,0	97,8±3,7	108,2±2,6*	110,5±2,3*	120,2±2,5*

TAB.2 : Fréquence cardiaque (battements/min), rat vigile

Traitement	avant traitement	avant nicotine	nicotine 30 µg/kg	nicotine 50 µg/kg	nicotine 100 µg/kg
véhicule (n=7)	414±13	386±11	426±14	436±18	457±18
béfloxatone (n=7)	397±13	368±18	399±12	390±9*	399±8**

TAB.3 : Pression artérielle moyenne (mm Hg), rat vigile

Traitement	avant traitement	avant nicotine	nicotine 30 µg/kg	nicotine 50 µg/kg	nicotine 100 µg/kg
véhicule (n=6)	113,7±3,3	114,2±4,0	138,7±5,7	133,3±5,4	150,3±5,8
Moclobémide (n=6)	105,7±2,3 NS	99,8±2,6 NS	111,8±2,6***	113,7±3,3*	123,9±3,9***

TAB.4 : Fréquence cardiaque (battements/min), rat vigile

Traitement	avant traitement	avant nicotine	nicotine 30 µg/kg	nicotine 50 µg/kg	nicotine 100 µg/kg
véhicule (n=6)	430±36	410±21	470±20	467±15	470±21
Moclobémide (n=6)	430±11 NS	383±17 NS	412±25 NS	410±27 NS	438±25 NS

moyenne ± ESM

NS : non significativement différent du groupe véhicule (P>0,05, test de Dunnett après analyse de variance à deux facteurs avec mesures répétées)

* : significativement différent du groupe véhicule (P≤0,05, test de Dunnett après analyse de variance à 2 facteurs avec mesures répétées)

** : significativement différent du groupe véhicule (P≤0,01, test de Dunnett après analyse de variance à 2 facteurs avec mesures répétées)

*** : significativement différent du groupe véhicule (P≤0,001, test de Dunnett après analyse de variance à 2 facteurs avec mesures répétées)

EXEMPLES DE COMPOSITIONS PHARMACEUTIQUES

Exemple 1 : comprimé contenant de la befloxatone et patch transdermique contenant de la nicotine

On fabrique des comprimés contenant 10 mg de befloxatone selon la composition suivante

befloxatone	5,0 %
lactose 150 mesh	66,0 %
cellulose microcristalline	20,0 %
povidone	4,0 %
crospovidone	4,0 %
stéarate de magnesium	1,0 %

Les cinq premiers composants sont mélangés, granulés avec de l'eau, séchés et calibrés. Les granulés sont ensuite mélangés au stéarate de magnésium et compressés pour former des comprimés de 200 mg en masse, à l'aide d'une presse rotative.

On prépare un patch transdermique d'une surface de 20 cm^2 capable de libérer 14 mg en 24 heures selon la composition suivante :

Couche matricielle :
- S(-)nicotine 35 mg
- polymère acrylique Duro-Tak 387-2353
- promoteur d'absorption triglycéride Miglyol 812
- copolymère méthacrylique Eudragit E100

Couche support :
- film polyester (Paratex III/40)

Couche adhésive :
- polymère acrylique auto-adhésif Duro-Tak 387-2353
- promoteur d'absorption triglycéride Miglyol 812

Exemple 2 : Comprimé bicouche contenant de la befloxatone et de la nicotine

Les granulés sont préparés par granulation humide selon les compositions suivantes :

GRANULE 1	
béfloxatone	5 %
lactose 150 mesh	66 %
cellulose microcristalline	20 %
povidone	4 %
crospovidone	4 %
stéarate de magnésium	1 %
GRANULE 2	
nicotine polacrylix	qsp 5% nicotine
lactose 150 mesh	*qsp* 100 %
cellulose microcristalline	20 %
povidone	4 %
hydroxypropylméthylcellulose	25 %
stéarate de magnesium	1 %

Les cinq premiers composants de chaque granulé sont mélangés, granulés avec de l'eau, puis les granulés obtenus sont séchés et calibrés. Le stéarate de magnésium est ensuite ajouté et mélangé. Des comprimés bicouches sont préparés par compression en utilisant une presse Manesty BL. Chaque couche contient 100 mg de granulé si bien que chaque comprimé contient 5 mg de béfloxatone et 5 mg de nicotine.

Exemple 3 : Capsule contenant de la béfloxatone et spray nasal contenant de la nicotine

Les comprimés contenant 10 mg de béfloxatone sont préparés selon la composition suivante :

béfloxatone	6,25 %
lactose 150 mesh	84,15 %
povidone	4,00 %
crospovidone	5,00 %
stéarate de magnésium	0,50 %
silice colloïdale	0,10 %

Les cinq premiers composants de chaque granulé sont mélangés, granulés avec de l'eau, séchés et calibrés. Les granulés sont ensuite mélangés avec le stéarate de magnésium et la silice colloïdale puis on remplit des capsules en gélatine de taille 2 de 160 mg des granulés ainsi préparés.

On prépare une solution pour administration nasale contenant 50 mg de nicotine, 900 mg de chlorure de sodium, 10 mg de chlorure de benzalkonium, 100 mg de EDTA sodium et 100 mg d'eau stérilisée. Cette solution est filtrée et distribuée dans des ampoules.

Revendications

1. Composition pharmaceutique comprenant de la nicotine ou un ligand des récepteurs nicotiniques et un inhibiteur de la monoamine oxydase comme produit de combinaison pour une utilisation simultanée, séparée ou étalée dans le temps destiné au sevrage tabagique.

2. Composition pharmaceutique comprenant de la nicotine ou un ligand des récepteurs nicotiniques et un inhibiteur de la monoamine oxydase A ou A,B mixte réversible comme produit de combinaison pour une utilisation simultanée, séparée ou étalée dans le temps destinée au sevrage tabagique.

3. Composition pharmaceutique selon l'un quelconque des revendications 1 ou 2, caractérisée en ce que l'inhibiteur de la monoamine oxydase est choisi dans le groupe constitué par :

- parmi les IMAO de type A : la béfloxatone, le moclobémide, la brofaromine, la phénoxathine, l'esuprone, le befol, le RS 8359 (Sankyo), le T794 (Tanabé), le KP 9 (Krenitsky, USA), le E 2011 (Eisei), la toloxatone, le pirlindole, l'amiflamine, la sercloremine, la bazinaprine, la (-)3-[2-(3,3,3-trifluoropropyl)-3,4-dihydro-2*H*-1-benzopyran-6-yl]-5(*R*)-méthoxyméthyloxazolidin-2-one, la 3-(2-propylbenzofuran-5-yl)-5(*R*)-méthoxyméthyloxazolidin-2-one et la 3-[2-(3,3,3-trifluoropropyl)-2,3-dihydrobenzofuran-5-yl]-5(*R*)-méthoxyméthyloxazolidin-2-one,
- parmi les IMAO de type B : le lazabemide, le milacémide, la caroxazone, l'IFO, le L-deprényl, la mofégiline, la rasagéline, la pargyline, la (*S*)-5-méthoxyméthyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one et la 5-[4-(4,4,4-trifluorobutoxy)phényl]-3-(2-méthoxyéthyl)-1,3,4-oxadiazol-2(3*H*)-one,
- parmi les IMAO de type A,B mixte : la [3(*S*),3*a*(*S*)]-3-méthoxyméthyl-7-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)-3,3*a*,4,5-tétrahydro-1*H*-oxazolo[3,4-*a*]quinoléin-1-one, la

[3(*S*),3*a*(*S*)]3-méthoxyméthyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tétrahydro-1*H*-oxazolo[3,4-a]quinoléine-1-one, la (*R*)-5-(méthoxyméthyl)-3-[6-(4,4,4-triflurobutoxy) benzofuran-3-yl]oxazolidin-2-one, le (*R*)-5-méthoxyméthyl-3-(6-cyclopropylméthoxybenzofuran-3-yl)oxazolidin-2-one, la 3-[2-(3,3,3-trifluoropropyl)benzofuran-5-yl]-5(*S*)-méthoxyméthyloxazolidin-2-one et la 3-(2-phénylbenzofuran-5-yl)-5(*S*)-méthoxyméthyloxazolidin-2-one.

4. Composition pharmaceutique selon l'une quelconque des revendications 1 à 3, caractérisée en ce qu'elle est destinée à l'administration par voie orale, nasale, parentérale, transdermique ou mixte.

5. Composition pharmaceutique selon la revendication 4, caractérisée en ce que l'un au moins ou bien de l'inhibiteur de la monoamine oxydase ou bien de la nicotine ou un récepteur des ligands nicotiniques est destinée à l'administration transdermique.

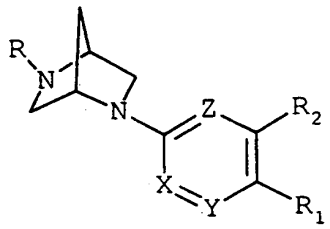
6. Composition pharamceutique selon la revendication 5, caractérisée en ce que l'administration transdermique est réalisée par patch ou timbre transdermique.

7. Composition pharmaceutique selon l'une quelconque des revendications 1 à 6, caractérisée en ce que le lignand des récepteurs nicotiniques est choisi parmi les agonistes des récepteurs nicotiniques suivants : la cytisine, la lobéline, l'ABT-418, l'épibatidine, le GTS-21, le AR-R17779, le ABT-594, le ABT-089, mais aussi les agonistes ou antagonistes nicotiniques suivants :
le AN-072, l'eperisone, le bromure de rapacuronium, l'altinicline, le conantokin-G, le GW-280430, le RJR-2403, la galantamine, le SIB 1553 A, le A-85380, la métanicotine, le RJR-2531, le RJR-2557, le DBO-83, la 9-bromo-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one, la 11-fluoro-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one, la

9-phényl-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one, la 9-benzyl-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one, la 9-acétyl-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one, la 9-(2-pyridyl)-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one, 9-(2,4-difluorophényl)-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one, la 9-(2-thiazolyl)-1,2,3,4,5,6-hexahydro-8H-1,5-méthanopyrido[1,2-a][1,5]diazocin-8-one, l'endo-6-(3-pyridyl)-2-azabicyclo[2.2.2]octane, l'endo-6-(5-pyrimidinyl)-2-azabicyclo[2.2.2]octane, le 6-(5-bromo-3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ène, le 6-(5-éthynyl-3-pyridyl)-2-azabicyclo[2.2.2]octane, le (±)-8-méthyl-3-(3-pyridyl)-8-azabicyclo[3.2.1]oct-2-ene, le (±)-8-(benzyl)-3-(3-pyridyl)-8-azabicyclo[3.2.1]oct-2-ène, le (±)-3-(6-chloro-3-pyridinyl)-8-méthyl-8-azabicyclo[3.2.1]oct-2-ene, le (±)-3-(8-méthyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)aniline, la spiro[1,3-benzodioxole-2,3'-quinuclidine], la 5-méthylspiro[1,3-benzodioxole-2,3'-quinuclidine], la 5-tert-butylspiro[1,3-benzodioxole-2,3'-quinuclidine], la (±)-3-(5-méthoxy-3-pyridinyl)-9-azabicyclo[3.3.1]non-2-ène, la (±)-3-(5-méthoxy-3-pyridinyl)-9-méthyl-9-azabicyclo[3.3.1]non-2-ène, la (±)-3-(9-méthyl-9-azabicyclo[3.3.1]non-2-èn-3-yl)phénylamine, le (±)-3-(3-pyridinyl)-9-azabicyclo[3.3.1]non-2-ène, la (±)-9-méthyl-3-(3-pyridinyl)-9-azabicyclo[3.3.1]non-2-ène, le spiro[1-azabicyclo[2.2.2]octane-3-2'(3'H)-furo[2,3-b]pyridine]7'-oxide, la 1-(6-chloro-5-méthoxypyridin-3-yl)perhydro-1,4-diazépine, la 1-(5-méthoxypyridine-3-yl)perhydro-1,4-diazépine, la 1-(5-méthoxypyridin-3-yl)perhydro-1,5-diazocine, la 3-(perhydro-1,4-diazépin-1-yl)quinoline, la 1-(6-bromopyridin-3-yl)perhydro-1,4-diazépine, la 1-(5-propoxypyridin-3-yl)perhydro-1,4-diazépine, la 4-(3-pyridinyloxy)perhydroazépine, la 2-méthyl-1,2,3,5,6,7,8,9-octahydro-5,9-méthanopyrrolo

[3,4-h][3]benzazépine-1,3-dione, la 1,3-diméthyl-1,2,3,5,6,7,8,9-octahydro-5,9-méthanoimidazo [4,5-h][3]benzazépin-2-one, la 1,2,3,5,6,7,8,9-octahydro-5,9-méthanopyrrolo[3,4-h][3] benzazépine-1,3-dione, la 7,8-difluoro-2,3,4,5-tétrahydro-1H-1,5-méthano-3-benzazépine, le 8-éthynyl-2,3,4,5-tétrahydro-1H-1,5-méthano-3-benzazépine-7-carbonitrile, la 7-chloro-8-(trifluorométhyl)-2,3,4,5-tétrahydro-1H-1,5-méthano-3-benzazépine, le 8-(trifluorométhyl)-2,3,4,5-tétrahydro-1H-1,5-méthano-3-benzazépine-7-carbonitrile, les composés (*R*,*R*), (*S*,*S*), (*R*,*S*) et (*S*,*R*) de la 2-pyrrolidin-2-yl-2,3-dihydrofuro[3,2-*b*]pyridine et de la 6-pyrrolidin-2-yl-6,7-dihydro-5*H*-2-pyrindine ainsi que

- les composés répondant à la formule générale (I)



(I)

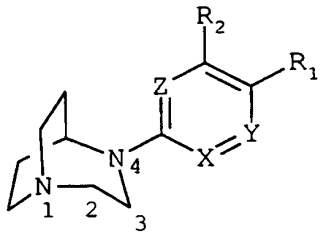
dans laquelle

l'un des symboles X, Y et Z représente un atome d'azote, un autre représente un groupe de formule C-R_3 et le troisième représente un atome d'azote ou un groupe de formule C-R_4,

R_3 et R_4 représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou d'halogène ou un groupe trifluorométhyle, cyano, hydroxy, (C_1-C_6)alkyle ou (C_1-C_6)alcoxy,

R_1 et R_2 représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou d'halogène ou un groupe trifluorométhyle, cyano, hydroxy, (C_1-C_6)alkyle, (C_1-C_6)-alcoxy, ou phényle éventuellement substitué par un ou deux atomes d'halogènes, par un ou deux groupes trifluoro-méthyle, par un groupe cyano, par un groupe nitro, par un groupe hydroxy, par un groupe (C_1-C_6)alkyle, par un ou deux groupes (C_1-C_6)alcoxy, par un groupe méthylènedioxy, par un groupe acétyle, par un groupe trifluorométhoxy ou par un

groupe méthylthio,
R représente un atome d'hydrogène ou un groupe (C_1-C_6)alkyle,
étant toutefois exclus les composés de formule générale (I) dans laquelle X représente un groupe de formule CH, Y et Z représentent chacun un atome d'azote, et R_1 ou R_2 ne représente pas un groupe phényle éventuellement substitué,
- et les composés répondant à la formule générale (I)



(I)

dans laquelle
l'un des symboles X, Y et Z représente un atome d'azote, un autre représente un groupe de formule C-R_3 et le troisième représente un atome d'azote ou un groupe de formule C-R_4,
R_3 et R_4 représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou d'halogène ou un groupe trifluorométhyle, cyano, hydroxy, (C_1-C_6)alkyle ou (C_1-C_6)alcoxy,
R_1 et R_2 représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou d'halogène ou un groupe trifluorométhyle, cyano, hydroxy, (C_1-C_6)alkyle, (C_1-C_6)alcoxy, ou phényle éventuellement substitué par un atome d'halogène, par un ou deux groupes trifluorométhyle, par un groupe cyano, par un groupe nitro, par un groupe hydroxy, par un groupe (C_1-C_6)alkyle, par un groupe (C_1-C_6)alcoxy, par un groupe acétyle, par un groupe méthylènedioxy, par un groupe trifluorométhoxy, par un groupe méthylthio ou par un groupe phényle.

8. Composition pharmaceutique selon la revendication 4, caractérisée en ce que l'inhibiteur de la monoamine oxydase est la béfloxatone.

9. Composition pharmaceutique selon la revendication 4, caractérisée en ce que l'inhibiteur de la monoamine oxydase est le moclobémide.

10. Composition pharmaceutique selon la revendication 4, caractérisée en ce que l'inhibiteur de la monoamine oxydase est la (*S*)-5-méthoxyméthyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

11. Composition pharmaceutique selon la revendication 4, carctérisée en ce que l'inhibiteur de la monoamine oxydase est la [3(*S*),3*a*(*S*)]-3-méthoxyméthyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tétrahydro-1*H*-oxazolo[3,4-a] quinoléine-1-one.

12. Composition pharamceutique selon la revendication 4, caractérisée en ce que l'inhibiteur de la monoamine oxydase est la [3(*S*),3*a*(*S*)]-3-méthoxyméthyl-7-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)-3,3*a*,4,5-tétrahydro-1*H*-oxazolo[3,4-*a*]quinoléin-1-one.

13. Composition pharmaceutique comprenant de la nicotine ou un ligand des récepteurs nicotiniques et un inhibiteur de la monoamine oxydase.

14. Composition pharmaceutique selon la revendication 13, caractérisée en ce que l'inhibiteur de la monoamine oxydase est de type A ou A,B mixte réversible.

15. Composition pharmaceutique selon l'une quelconque des revendications 1 à 14, pour une utilisation simultanée dans le temps, caractérisée en ce qu'elle se présente selon l'une des formes pharmaceutiques suivantes : comprimé, pilules, gélule, gomme à mâcher à libération immédiate ou prolongée, timbre transdermique ou patch, spray nasal ou pulmonaire, solution ou suspension injectable ou bien suppositoire.

16. Utilisation d'une association de nicotine ou un ligand des récepteurs nicotiniques et d'un inhibiteur de la monoamine oxydase pour la fabrication d'un médicament destiné au sevrage tabagique.

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/FR 00/00193

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/535 A61K31/465 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 803 081 A (WILLIAMS JONNIE R ET AL) 8 September 1998 (1998-09-08) cited in the application column 2, line 40 -column 3, line 24 column 4, line 13 - line 29 ---	1,2,4, 13-16
A	CINCIRIPINI P.M. ET AL: "Smoking cessation: Recent developments in behavioral and pharmacologic interventions." ONCOLOGY, (1998) 12/2 (249-260+265-270)., XP002121187 page 252, column 1, paragraph 4 -page 254, column 1, paragraph 2 page 255, column 3, paragraph 3 -column 4, paragraph 1 --- -/--	1-16

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 2000	23/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Leherte, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/FR 00/00193

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 28934 A (HOFFMANN LA ROCHE ;ASSIST PUBL HOPITAUX DE PARIS (FR); AMREIN ROMA) 2 November 1995 (1995-11-02) cited in the application abstract; claims	1-16

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FR 00/00193

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: -
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See supplemental sheet INFORMATION FOLLOW-UP PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Claims 1-16 of the present application concern a pharmaceutical composition defined (inter alia) by means of the following parameters: "ligand of nicotine receptors" and "monoamine oxydase inhibitor".
In the present context, the use of said parameters is considered as leading to a lack of clarity as defined by PCT Article 6. It is impossible to compare the parameters which the applicant has chosen to use with what is disclosed in prior art. The resulting lack of clarity is such that it is not possible to carry out any exhaustive and significant search. Consequently, the search was carried out on the basis of the general inventive concept of the application and limited to those compositions mentioned in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, concerning inventions in respect of which no search report has been established need not be the subject of a preliminary examination report (PCT Rule 66.1 (e)). The applicant is advised that the guideline adopted by the EPO acting in its capacity as International Preliminary Examining Authority is not to proceed with a preliminary examination of a subject matter unless a search has been carried out thereon. This position will remain unchanged, notwithstanding that the claims have or have not been modified, either after receiving the search report, or during any procedure under Chaper II.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. .onal Application No
PCT/FR 00/00193

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5803081 A	08-09-1998	US 5845647 A	08-12-1998
		AU 4048297 A	25-02-1998
		BR 9711622 A	18-01-2000
		CA 2262866 A	12-02-1998
		CN 1231583 A	13-10-1999
		EP 0967898 A	05-01-2000
		WO 9805226 A	12-02-1998
WO 9528934 A	02-11-1995	AU 2446895 A	16-11-1995

RAPPORT DE RECHERCHE INTERNATIONALE

De de internationale No
PCT/FR 00/00193

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 7 A61K45/06 A61K31/535 A61K31/465 A61K31/42

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 7 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	US 5 803 081 A (WILLIAMS JONNIE R ET AL) 8 septembre 1998 (1998-09-08) cité dans la demande colonne 2, ligne 40 -colonne 3, ligne 24 colonne 4, ligne 13 - ligne 29 ---	1,2,4, 13-16
A	CINCIRIPINI P.M. ET AL: "Smoking cessation: Recent developments in behavioral and pharmacologic interventions." ONCOLOGY, (1998) 12/2 (249-260+265-270)., XP002121187 page 252, colonne 1, alinéa 4 -page 254, colonne 1, alinéa 2 page 255, colonne 3, alinéa 3 -colonne 4, alinéa 1 --- -/--	1-16

[X] Voir la suite du cadre C pour la fin de la liste des documents

[X] Les documents de familles de brevets sont indiqués en annexe

° Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
15 mai 2000	23/05/2000

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Leherte, C

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Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

De de internationale No
PCT/FR 00/00193

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indicationdes passages pertinents	no. des revendications visées
A	WO 95 28934 A (HOFFMANN LA ROCHE ;ASSIST PUBL HOPITAUX DE PARIS (FR); AMREIN ROMA) 2 novembre 1995 (1995-11-02) cité dans la demande abrégé; revendications	1-16

1

Formulaire PCT/ISA/210 (suite de la deuxième feuille) (juillet 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale n°
PCT/FR 00/00193

Cadre I Observations – lorsqu'il a été estimé que certaines revendications ne pouvaient pas faire l'objet d'une recherche (suite du point 1 de la première feuille)

Conformément à l'article 17.2)a), certaines revendications n'ont pas fait l'objet d'une recherche pour les motifs suivants:

1. ☐ Les revendications n[os]
se rapportent à un objet à l'égard duquel l'administration n'est pas tenue de procéder à la recherche, à savoir:

2. ☒ Les revendications n[os] –
se rapportent à des parties de la demande internationale qui ne remplissent pas suffisamment les conditions prescrites pour qu'une recherche significative puisse être effectuée, en particulier:
Voir feuille supplémentaire SUITE DES RENSEIGNEMENTS PCT/ISA/210

3. ☐ Les revendications n[os]
sont des revendications dépendantes et ne sont pas rédigées conformément aux dispositions de la deuxième et de la troisième phrases de la règle 6.4.a).

Cadre II Observations – lorsqu'il y a absence d'unité de l'invention (suite du point 2 de la première feuille)

L'administration chargée de la recherche internationale a trouvé plusieurs inventions dans la demande internationale, à savoir:

1. ☐ Comme toutes les taxes additionnelles ont été payées dans les délais par le déposant, le présent rapport de recherche internationale porte sur toutes les revendications pouvant faire l'objet d'une recherche.

2. ☐ Comme toutes les recherches portant sur les revendications qui s'y prêtaient ont pu être effectuées sans effort particulier justifiant une taxe additionnelle, l'administration n'a sollicité le paiement d'aucune taxe de cette nature.

3. ☐ Comme une partie seulement des taxes additionnelles demandées a été payée dans les délais par le déposant, le présent rapport de recherche internationale ne porte que sur les revendications pour lesquelles les taxes ont été payées, à savoir les revendications n [os]

4. ☐ Aucune taxe additionnelle demandée n'a été payée dans les délais par le déposant. En conséquence, le présent rapport de recherche internationale ne porte que sur l'invention mentionnée en premier lieu dans les revendications; elle est couverte par les revendications n [os]

Remarque quant à la réserve

☐ Les taxes additionnelles étaient accompagnées d'une réserve de la part du déposant.

☐ Le paiement des taxes additionnelles n'était assorti d'aucune réserve.

SUITE DES RENSEIGNEMENTS INDIQUES SUR PCT/ISA/ 210

Suite du cadre I.2

Les revendications 1-16 présentes ont trait à une composition pharmaceutique définie (entre autres) au moyen des paramètres suivants: "ligand des récepteurs nicotiniques" et "inhibiteur de la monoamine oxydase".
L'utilisation de ces paramètres est considérée , dans le présent contexte, comme menant à un manque de clarté au sens de l'Article 6 PCT. Il est impossible de comparer les paramètres que le déposant a choisi d'utiliser avec ce qui est révélé dans l'état de la technique. Le manque de clarté qui en découle est tel q'une recherche significative complète est impossible. Par conséquent, la recherche a été effectué selon l'idée inventive générale de la demande et a été limitée aux compositions mentionnés dans les exemples de la description.

L'attention du déposant est attirée sur le fait que les revendications, ou des parties de revendications, ayant trait aux inventions pour lesquelles aucun rapport de recherche n'a été établi ne peuvent faire obligatoirement l'objet d'un rapport préliminaire d'examen (Règle 66.1(e) PCT). Le déposant est averti que la ligne de conduite adoptée par l'OEB agissant en qualité d'administration chargée de l'examen préliminaire international est, normalement, de ne pas procéder à un examen préliminaire sur un sujet n'ayant pas fait l'objet d'une recherche. Cette attitude restera inchangée, indépendamment du fait que les revendications aient ou n'aient pas été modifiées, soit après la réception du rapport de recherche, soit pendant une quelconque procédure sous le Chapitre II.

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Dem. de Internationale No
PCT/FR 00/00193

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
US 5803081 A	08-09-1998	US 5845647 A	08-12-1998
		AU 4048297 A	25-02-1998
		BR 9711622 A	18-01-2000
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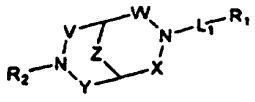
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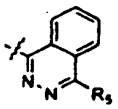
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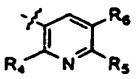
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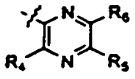
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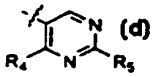
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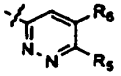
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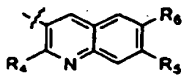
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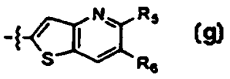
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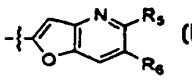
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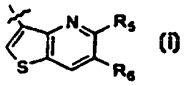
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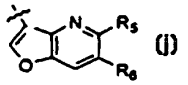
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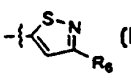
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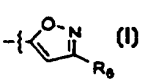
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(57) Abstract

Compounds of formula (I) or a pharmaceutically acceptable salt thereof wherein: V is selected from the group consisting of a covalent bond and CH_2; W is selected from the group consisting of a covalent bond, CH_2 and CH_2CH_2; X is selected from the group consisting of a covalent bond and CH_2; Y is selected from the group consisting of a covalent bond, CH_2, and CH_2CH_2; Z is selected from the group consisting of CH_2, CH_2CH_2, and $CH_2CH_2CH_2$; L_1 is selected from the group consisting of a covalent bond and $(CH_2)_n$; n is 1–5; R_1 is selected from the group consisting of (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), and (l); R_2 is selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, aminoalkyl, aminocarbonylalkyl, benzyloxycarbonyl, cyanoalkyl, dihydro–3–pyridinylcarbonyl, hydroxy, hydroxyalkyl, phenoxycarbonyl, and $–NH_2$; are useful for controlling synaptic transmission in mammal.

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DIAZABICYCLIC DERIVATIVES AS NICOTINIC ACETYLCHOLINE RECEPTOR LIGANDS

FIELD OF THE INVENTION

The present invention is directed to a series of N-substituted diazabicyclic compounds, methods for selectively controlling neurotransmitter release in mammals using these compounds, and pharmaceutical compositions containing these compounds.

BACKGROUND OF THE INVENTION

Compounds that selectively control chemical synaptic transmission offer therapeutic utility in treating disorders that are associated with dysfunctions in synaptic transmission. This utility may arise from controlling either pre-synaptic or post-synaptic chemical transmission. The control of synaptic chemical transmission is, in turn, a direct result of a modulation of the excitability of the synaptic membrane. Presynaptic control of membrane excitability results from the direct effect an active compound has upon the organelles and enzymes present in the nerve terminal for synthesizing, storing, and releasing the neurotransmitter, as well as the process for active re-uptake. Postsynaptic control of membrane excitability results from the influence an active compound has upon the cytoplasmic organelles that respond to neurotransmitter action.

An explanation of the processes involved in chemical synaptic transmission will help to illustrate more fully the potential applications of the invention. (For a fuller explanation of chemical synaptic transmission refer to Hoffman et al., "Neuro-transmission: The autonomic and somatic motor nervous systems." In: Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th ed., J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon, and A. Goodman Gilman, eds., Pergamon Press, New York, (1996), pp. 105-139).

Typically, chemical synaptic transmission begins with a stimulus that depolarizes the transmembrane potential of the synaptic junction above the threshold that elicits an

all-or-none action potential in a nerve axon. The action potential propagates to the nerve terminal where ion fluxes activate a mobilization process leading to neurotransmitter secretion and "transmission" to the postsynaptic cell. Those cells which receive communication from the central and peripheral nervous systems in the form of neurotransmitters are referred to as "excitable cells." Excitable cells are cells such as nerves. smooth muscle cells, cardiac cells and glands. The effect of a neurotransmitter upon an excitable cell may be to cause either an excitatory or an inhibitory postsynaptic potential (EPSP or IPSP, respectively) depending upon the nature of the postsynaptic receptor for the particular neurotransmitter and the extent to which other neurotransmitters are present. Whether a particular neurotransmitter causes excitation or inhibition depends principally on the ionic channels that are opened in the postsynaptic membrane (i.e., in the excitable cell).

EPSPs typically result from a local depolarization of the membrane due to a generalized increased permeability to cations (notably Na^+ and K^+), whereas IPSPs are the result of stabilization or hyperpolarization of the membrane excitability due to a increase in permeability to primarily smaller ions (including K^+ and Cl^-). For example, the neurotransmitter acetylcholine excites at skeletal muscle junctions by opening permeability channels for Na^+ and K^+. At other synapses, such as cardiac cells, acetylcholine can be inhibitory , primarily resulting from an increase in K^+ conductance.

The biological effects of the compounds of the present invention result from modulation of a particular subtype of acetylcholine receptor. It is, therefore, important to understand the differences between two receptor subtypes. The two distinct subfamilies of acetylcholine receptors are defined as nicotinic acetylcholine receptors and muscarinic acetylcholine receptors. (See Goodman and Gilman's, The Pharmacological Basis of Therapeutics, op. cit.).

The responses of these receptor subtypes are mediated by two entirely different classes of second messenger systems. When the nicotinic acetylcholine receptor is activated, the response is an increased flux of specific extracellular ions (e.g. Na^+, K^+ and Ca^{++}) through the neuronal membrane. In contrast, muscarinic acetylcholine receptor activation leads to changes in intracellular systems that contain complex molecules such as G-proteins and inositol phosphates. Thus, the biological consequences of nicotinic

acetylcholine receptor activation are distinct from those of muscarinic receptor activation. In an analogous manner, inhibition of nicotinic acetylcholine receptors results in still other biological effects, which are distinct and different from those arising from muscarinic receptor inhibition

As indicated above, the two principal sites to which drug compounds that affect chemical synaptic transmission may be directed are the presynaptic membrane and the post-synaptic membrane. Actions of drugs directed to the presynaptic site may be mediated through presynaptic receptors that respond to the neurotransmitter which the same secreting structure has released (i.e., through an autoreceptor), or through a presynaptic receptor that responds to another neurotransmitter (i.e., through a heteroreceptor). Actions of drugs directed to the postsynaptic membrane mimic the action of the endogenous neurotransmitter or inhibit the interaction of the endogenous neurotransmitter with a postsynaptic receptor.

Classic examples of drugs that modulate postsynaptic membrane excitability are the neuromuscular blocking agents which interact with nicotinic acetylcholine-gated channel receptors on skeletal muscle, for example, competitive (stabilizing) agents, such as curare, or depolarizing agents, such as succinylcholine.

In the central nervous system, postsynaptic cells can have many neurotransmitters impinging upon them. This makes it difficult to know the precise net balance of chemical synaptic transmission required to control a given cell. Nonetheless, by designing compounds that selectively affect only one pre- or postsynaptic receptor, it is possible to modulate the net balance of all the other inputs. Obviously, the more that is understood about chemical synaptic transmission in CNS disorders, the easier it would be to design drugs to treat such disorders.

Knowing how specific neurotransmitters act in the CNS allows one to predict the disorders that may be treatable with certain CNS-active drugs. For example, dopamine is widely recognized as an important neurotransmitter in the central nervous systems in humans and animals. Many aspects of the pharmacology of dopamine have been reviewed by Roth and Elsworth, "Biochemical Pharmacology of Midbrain Dopamine Neurons", In: Psychopharmacology: The Fourth Generation of Progress, F.E. Bloom and D.J. Kupfer, Eds., Raven Press, NY, 1995, pp 227-243). Patients with Parkinson's

disease have a primary loss of dopamine containing neurons of the nigrostriatal pathway, which results in profound loss of motor control. Therapeutic strategies to replace the dopamine deficiency with dopamine mimetics, as well as administering pharmacologic agents that modify dopamine release and other neurotransmitters have been found to have therapeutic benefit ("Parkinson's Disease", In: Psychopharmacology: The Fourth Generation of Progress, op. cit., pp 1479-1484).

New and selective neurotransmitter controlling agents are still being sought, in the hope that one or more will be useful in important, but as yet poorly controlled, disease states or behavior models. For example, dementia, such as is seen with Alzheimer's disease or Parkinsonism, remains largely untreatable. Symptoms of chronic alcoholism and nicotine withdrawal involve aspects of the central nervous system, as does the behavioral disorder Attention-Deficit Disorder (ADD). Specific agents for treatment of these and related disorders are few in number or non-existent.

A more complete discussion of the possible utility as CNS-active agents of compounds with activity as cholinergic ligands selective for neuronal nicotinic receptors, (i.e., for controlling chemical synaptic transmission) may be found in U.S. Patent 5,472,958, to Gunn et al., issued Dec. 5, 1995, which is incorporated herein by reference.

Existing acetylcholine agonists are therapeutically suboptimal in treating the conditions discussed above. For example, such compounds have unfavorable pharmacokinetics (e.g., arecoline and nicotine), poor potency and lack of selectivity (e.g., nicotine), poor CNS penetration (e.g., carbachol) or poor oral bioavailability (e.g., nicotine). In addition, other agents have many unwanted central agonist actions, including hypothermia, hypolocomotion and tremor and peripheral side effects, including miosis, lachrymation, defecation and tachycardia (Benowitz et al., in: Nicotine Psychopharmacology, S. Wonnacott, M.A.H. Russell, & I.P. Stolerman, eds., Oxford University Press, Oxford, 1990, pp. 112-157; and M. Davidson, et al., in Current Research in Alzheimer Therapy, E. Giacobini and R. Becker, ed.; Taylor & Francis: New York, 1988; pp 333-336).

Williams et al. reports the use of cholinergic channel modulators to treat Parkinson's and Alzheimer's Diseases. M. Williams et al., "Beyond the Tobacco Debate: Dissecting Out the Therapeutic Potential of Nicotine", Exp. Opin. Invest. Drugs

5, pp. 1035-1045 (1996). Salin-Pascual et al. reports short-term improvement of non-smoking patients suffering from depression by treatment with nicotine patches. R. J.Salin-Pascual et al., "Antidepressant Effect of Transdermal Nicotine Patches in Non-Smoking Patients with Major Depression", J. Clin. Psychiatry, v. 57 pp. 387-389 (1996).

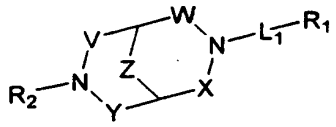
Some diazabicyclo[2.2.1]heptane derivatives have been disclosed for various purposes. For example, N-heteroaromatic, N-alkylaryl substituted diazabicyclo[2.2.1]heptanes have been disclosed in European Patent Application No. 0 400 661 for the prevention of disorders resulting from brain and/or spinal cord anoxia; N-heteroaromatic, N-alkylaryl diazabicyclo[2.2.1]heptane derivatives have been disclosed in European Patent Application 0 324 543 as antiarrhythmic agents; N-heteroaromatic, –alkylaryl diazabicyclo[2.2.1]heptane derivatives have been disclosed in European Patent Publication No. 0 345 808 B1 for the treatment of depression; N-alkylamidoheteroaromatic, N-alkylaromatic diazabicyclo[2.2.1] heptane derivatives have been disclosed in U.S. Patent No. 5,382,584 for effective anti-ischemic protection for CNS and cardiac tissue, di-N-acylheteroaromatic diazabicyclo[2.2.1] heptane derivatives have been disclosed in PCT Publication No. WO97/17961 to stimulate hematopoiesis and for the treatment of viral, fungal and bacterial infectious diseases. Moreover NH or N-methyl N-heteroaromatic diazabicyclo[2.2.1] heptane derivatives for treating central cholinergic disfunction have been disclosed in U.S. Patent No. 5,478,939. The heteroaromatic compounds can be halo-substituted pyrazines, thiazoles, thiadiazoles, thiophene or nitrobenzene, as disclosed in U.S. Patent No. 5,478,939.

Substituted diazabicyclo[3.2.1]octane derivatives have also been disclosed for various uses. For example, NH or N-alkyl, N-2-pyrimidinyl diazabicyclo[3.2.1] octane derivatives for sedatives have been disclosed in French Publication 2 531 709; N-acyl, –acylheteroaromatic diazabicyclo[3.2.1]octane derivatives have been disclosed in PCT Publication No. WO 95/23152 for cental analgesic activity, 3-[6-Cl-pyridazin-3-yl]-diazabicyclo[3.2.1]octane having antinociceptive effect was disclosed in Drug Development Research, 40:251-258 (1997); and NH, N-halosubstituted heteroaromatic diazabicyclo[3.2.1]octane derivatives as analgesics were disclosed in J.Med.Chem, 1998, 41, 674-681. However, there is still a need for even more effective N-substituted diazabicyclic compounds.

It is therefore an object of this invention to provide novel N-substituted diazabicyclic compounds. It is a further object of this invention to provide such compounds which selectively control neurotransmitter release.

SUMMARY OF THE INVENTION

The present invention discloses N-substituted diazabicyclic compounds, a method for selectively controlling neurotransmitter release in mammals using these compounds, and pharmaceutical compositions including those compounds. More particularly, the present invention is directed to compounds of formula I:



I,

and their pharmaceutically acceptable salts wherein:

V is selected from the group consisting of a covalent bond and CH_2;

W is selected from the group consisting of a covalent bond, CH_2, and CH_2CH_2;

X is selected from the group consisting of a covalent bond and CH_2;

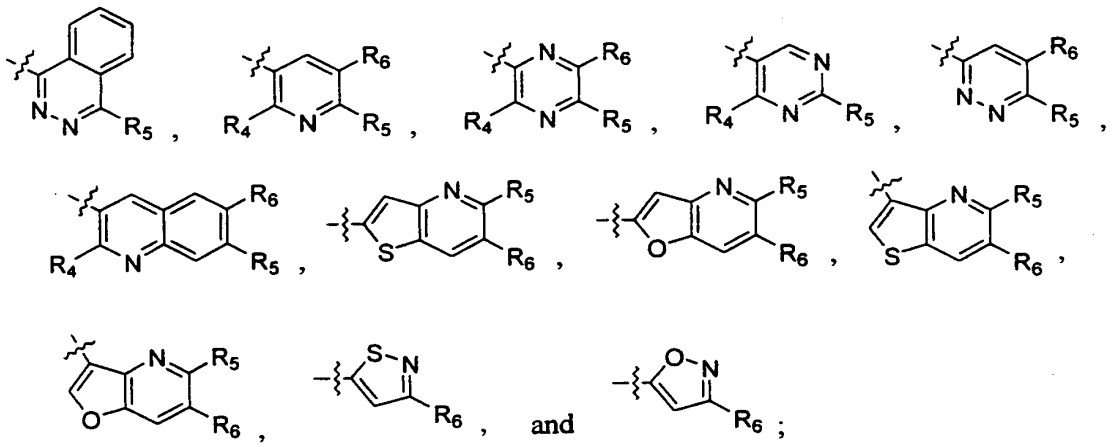
Y is selected from the group consisting of a covalent bond, CH_2, and CH_2CH_2;

Z is selected from the group consisting of CH_2, CH_2CH_2, and $CH_2CH_2CH_2$;

L_1 is selected from the group consisting of a covalent bond and $(CH_2)_n$;

n is 1-5;

R_1 is selected from the group consisting of



R_2 is selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, aminoalkyl, aminocarbonylalkyl, benzyloxycarbonyl, cyanoalkyl, dihydropyridin-3-ylcarbonyl, hydroxy, hydroxyalkyl, phenoxycarbonyl, and $-NH_2$;

R_4 is selected from the group consisting of hydrogen, alkyl, and halogen;

R_5 is selected from the group consisting of hydrogen, alkoxy, alkyl, halogen, nitro, and $-NH_2$;

R_6 is selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, mercapto, mercaptoalkyl, nitro, 5-tetrazolyl, $-NR_7SO_2R_8$, $-C(NR_7)NR_7R_8$, $-CH_2C(NR_7)NR_7R_8$, $-C(NOR_7)R_8$, $-C(NCN)R_7$, $-C(NNR_7R_8)R_8$, $-S(O)_2OR_7$, and $-S(O)_2R_7$; and

R_7 and R_8 are independently selected from the group consisting of hydrogen and alkyl;

with the proviso that the following compounds are excluded,

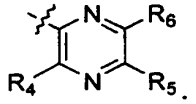
3-(6-chloro-3-pyridazinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-chloro-2-pyrazinyl)-3,8-diazabicyclo[3.2.1]octane;

8-(6-chloro-3-pyridazinyl)-3,8-diazabicyclo[3.2.1]octane; and

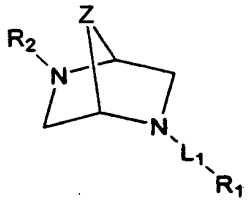
8-(6-chloro-2-pyrazinyl)-3,8-diazabicyclo[3.2.1]octane; and

with the further proviso that when V and X are each a covalent bond; W, Y, and Z are each CH_2; and L_1 is a covalent bond; then R_1 is other than



DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the present invention are disclosed compounds of formula II:



II,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2 and CH_2CH_2; and L_1, R_1, and R_2 are as defined in formula I.

Representative compounds of this embodiment include, but are not limited to:

(1S,4S)-2-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methyl-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(4-chloro-1-phthalazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(4-chloro-1-phthalazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methoxycarbonyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-pyrimidinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(3-quinolinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(3-methyl-5-isothiazolyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-amino-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-[5-(benzyloxy)-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-[5-hydroxy-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-nitro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

The following additional compounds, representative of formula II, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

(1S,4S)-2-(thieno[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(furo[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-3-pyridinyl)-5-cyanomethyl-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5,6-dichloro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-cyano-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-methoxy-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-bromo-6-chloro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-cyano-6-chloro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-hydroxymethyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane; (1S,4S)-2-(5-hydroxymethyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-hydroxymethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminomethyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminomethyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-carboxy-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-carboxy-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-carboxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminocarbonyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminocarbonyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-fluoro-5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(2-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-methyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminosulfonyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminosulfonyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminosulfonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(6-chloro-5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

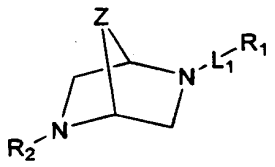
(1S,4S)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(5-bromo-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane; and

(1S,4S)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane.

In another embodiment of the present invention are disclosed compounds of formula III:



III,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2 and CH_2CH_2; and L_1, R_1, and R_2 are as defined in formula I.

Representative compounds of this embodiment include, but are not limited to:

(1R,4R)-2-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

2-(3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(thieno[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-3-pyridinyl)-5-cyanomethyl-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane; and

(1R,4R)-2-(3-pyridinylmethyl)-2,5-diazabicyclo[2.2.1]heptane.

The following additional compounds, representative of formula III, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

(1R,4R)-2-(furo[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-methyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-methyl-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(4-chloro-1-phthalazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(4-chloro-1-phthalazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-methoxycarbonyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-pyrimidinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(3-quinolinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(3-methyl-5-isothiazolyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-nitro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-amino-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-[5-(benzyloxy)-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-cyano-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-bromo-6-chloro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-cyano-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxymethyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxymethyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxymethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminomethyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminomethyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-carboxy-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-carboxy-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-carboxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminocarbonyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminocarbonyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-fluoro-5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(2-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-methyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

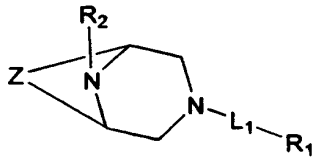
(1R,4R)-2-(5-aminosulfonyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminosulfonyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminosulfonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(6-chloro-5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(5-bromo-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1R,4R)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane; and
(1R,4R)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane.

In another embodiment of the present invention are disclosed compounds of formula IV:



IV,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2CH_2 and $CH_2CH_2CH_2$; and L_1, R_1, and R_2 are as defined in formula I.

Representative compounds of this embodiment include, but are not limited to:
3-(3-pyridazinyl)-3,8-diazabicyclo[3.2.1]octane;
3-(6-nitro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;
3-(6-amino-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;
3-(6-chloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane; and
3-(3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane.

The following additional compounds, representative of formula IV, may be prepared by one skilled in the art using known synthetic chemistry methodology or by

using synthetic chemistry methodology described in the Schemes and Examples contained herein.

3-(6-chloro-5-methyl-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5,6-dichloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-chloro-5-ethynyl-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-chloro-5-cyano-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-methoxy-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-fluoro-5-methyl-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-fluoro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-cyano-6-fluoro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

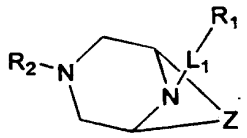
3-(5-bromo-6-chloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-aminomethyl-6-chloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-aminomethyl-6-fluoro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane; and

3-(5-aminomethyl-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane.

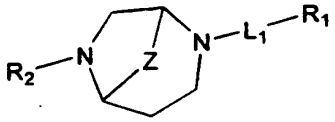
In another embodiment of the present invention are disclosed compounds of formula V:



V,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2CH_2 and $CH_2CH_2CH_2$; and L_1, R_1, and R_2 are as defined in formula I.

In another embodiment of the present invention are disclosed compounds of formula VI:



VI,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2 and CH_2CH_2; and L_1, R_1, and R_2 are as defined in formula I.

A representative compound of this embodiment includes, but is not limited to:

2-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane.

The following additional compounds, representative of formula VI, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

2-(3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-chloro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5,6-dichloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-chloro-5-cyano-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5-methoxy-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5-bromo-6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(6-chloro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(5,6-dichloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(6-chloro-5-cyano-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(5-methoxy-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

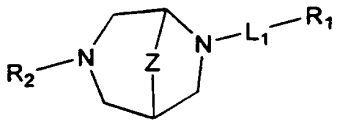
(1R,5S)-2-(6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane; and

(1R,5S)-2-(5-bromo-6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane.

In another embodiment of the present invention are disclosed compounds of formula VII:



VII,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2 and CH_2CH_2; and L_1, R_1, and R_2 are as defined in formula I.

The following compounds, representative of formula VII, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

(1R,5R)-6-(6-chloro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(5,6-dichloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(6-chloro-5-ethynyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(6-chloro-5-cyano-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(5-methoxy-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(6-fluoro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(5-ethynyl-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(5-cyano-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(5-bromo-6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-6-(6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-chloro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(5,6-dichloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-chloro-5-ethynyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-chloro-5-cyano-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(5-methoxy-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-fluoro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(5-ethynyl-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

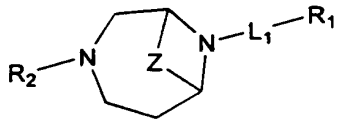
(1S,5S)-6-(5-cyano-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-6-(5-bromo-6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-6-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane; and

(1S,5S)-6-(6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane.

In another embodiment of the present invention are disclosed compounds of formula VIII:



VIII,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2CH_2 and $CH_2CH_2CH_2$; and L_1, R_1, and R_2 are as defined in formula I.

A representative compound of this embodiment includes, but is not limited to:

9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane.

The following additional compounds, representative of formula VIII, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

(1R,6S)-9-(6-chloro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(5,6-dichloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(6-chloro-5-ethynyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(6-chloro-5-cyano-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(5-methoxy-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(6-fluoro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(5-ethynyl-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(5-cyano-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

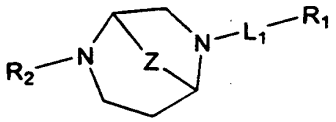
(1R,6S)-9-(5-bromo-6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-9-(6-chloro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5,6-dichloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-chloro-5-ethynyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-chloro-5-cyano-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5-methoxy-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-fluoro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5-ethynyl-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5-cyano-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5-bromo-6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane; and
(1S,6R)-9-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane.

In another embodiment of the present invention are disclosed compounds of formula IX:



IX,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2 and CH_2CH_2; and L_1, R_1, and R_2 are as defined in formula I.

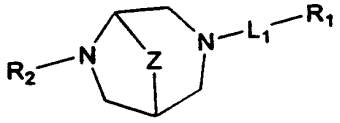
A representative compound of this embodiment includes, but is not limited to:
6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane.

The following additional compounds, representative of formula IX, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

(1R,5S)-6-(6-chloro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(5,6-dichloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(6-chloro-5-ethynyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(6-chloro-5-cyano-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(5-methoxy-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(6-fluoro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(5-ethynyl-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(5-cyano-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(5-bromo-6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1R,5S)-6-(3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(6-chloro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(5,6-dichloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(6-chloro-5-ethynyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(6-chloro-5-cyano-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(5-methoxy-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(6-fluoro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(5-ethynyl-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(5-cyano-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(5-bromo-6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane; and
(1S,5R)-6-(3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane.

In another embodiment of the present invention are disclosed compounds of formula X:



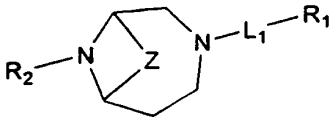
X,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2 and CH_2CH_2; and L_1, R_1, and R_2 are as defined in formula I.

The following compounds, representative of formula X, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

(1R,5R)-3-(6-chloro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5,6-dichloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-chloro-5-ethynyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-chloro-5-cyano-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5-methoxy-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-fluoro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5-cyano-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5-bromo-6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(6-chloro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(5,6-dichloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(6-chloro-5-ethynyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(6-chloro-5-cyano-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(5-methoxy-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(6-fluoro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(5-cyano-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(5-bromo-6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-3-(6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane; and
(1S,5S)-3-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane.

In another embodiment of the present invention are disclosed compounds of formula XI:



XI,

and their pharmaceutically acceptable salts wherein Z is selected from CH_2CH_2 and $CH_2CH_2CH_2$; and L_1, R_1, and R_2 are as defined in formula I.

Representative compounds of this embodiment include, but are not limited to:

3-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

9-methyl-3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane; and

3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane.

The following additional compounds, representative of formula XI, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

(1R,6S)-3-(6-chloro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(5,6-dichloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(6-chloro-5-ethynyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(6-chloro-5-cyano-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(5-methoxy-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(6-fluoro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(5-cyano-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(5-bromo-6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(6-chloro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(5,6-dichloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(6-chloro-5-ethynyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(6-chloro-5-cyano-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(5-methoxy-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(6-fluoro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

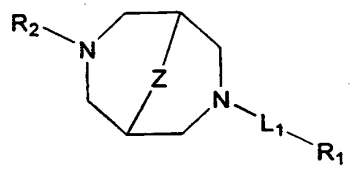
(1S,6R)-3-(5-cyano-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(5-bromo-6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1S,6R)-3-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane; and

(1S,6R)-3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane.

In another embodiment of the present invention are disclosed compounds of formula XII:



XII,

and their apharmaceutically acceptable salts wherein Z is selected from CH_2 and CH_2CH_2; and L_1, R_1, and R_2 are as defined in formula I.

Representative compounds of this embodiment include, but are not limited to:

3-(3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane and

3-(6-chloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane.

The following additional compounds, representative of formula XII, may be prepared by one skilled in the art using known synthetic chemistry methodology or by using synthetic chemistry methodology described in the Schemes and Examples contained herein.

3-(6-chloro-5-methyl-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(5,6-dichloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-chloro-5-ethynyl-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-chloro-5-cyano-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(5-methoxy-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-fluoro-5-methyl-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-fluoro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(5-cyano-6-fluoro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane; and

3-(5-bromo-6-chloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane.

Another embodiment of the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

Another embodiment of the present invention relates to a method for selectively controlling neurotransmitter release in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I.

Another embodiment of the present invention relates to a method of treating a disorder, such as Alzheimer's disease, Parkinson's disease, memory dysfunction, Tourette's syndrome, sleep disorders, attention deficit hyperactivity disorder, neurodegeneration, inflammation, neuroprotection, amyotrophic atral sclerosis, anxiety, depression, mania, schizophrenia, anorexia and other eating disorders, AIDS-induced dementia, epilepsy, urinary incontinence, Crohn's disease, migraines, premenstraul syndrome, erectile dysfunction, substance abuse, smoking cessation, inflammatory bowel syndrome, and pain, in a host mammal in need of such treatment comprising administering a therapeutically effective amount of a compound of formula I.

Definition of Terms

As used throughout this specification and the appended claims, the following terms have the following meanings.

The term "alkenyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 6 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, and 4-pentenyl.

The term "alkoxy," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein.

Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term "alkoxyalkoxy," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined herein. Representative examples of alkoxyalkoxy include, but are not limited to, tert-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, and methoxymethoxy.

The term "alkoxyalkyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, and methoxymethyl.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxycarbonylalkyl include, but are not limited to, 3-methoxycarbonylpropyl, 4-ethoxycarbonylbutyl, and 2-tert-butoxycarbonylethyl.

The term "alkyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, and neopentyl.

The term "alkylcarbonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and tert-butylcarbonyloxy.

The term "alkylthio," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylthio include, but are not limited, methylsulfanyl, ethylsulfanyl, tert-butylsulfanyl, and hexylsulfanyl.

The term "alkynyl," as used herein, refers to a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

The term "amino," as used herein, refers to $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are independently selected from hydrogen, alkyl, alkylcarbonyl, and formyl, as defined herein. Representative examples of amino include, but are not limited to, amino, methylamino, ethylmethylamino, methylisopropylamino, dimethylamino, diisopropylamino, diethylamino, formylamino, and acetylethylamino.

The term "aminoalkyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of aminoalkyl include, but are not limited to, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-amino-1-methylhexyl, and 2-(dimethylamino)ethyl.

The term "aminocarbonyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of aminocarbonyl include, but are not limited to, aminocarbonyl, dimethylaminocarbonyl, and ethylmethylaminocarbonyl.

The term "aminocarbonylalkyl," as used herein, refers to an aminocarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of aminocarbonylalkyl include, but are not limited to, 2-(aminocarbonyl)ethyl, 3-(dimethylaminocarbonyl)propyl, and ethylmethylaminocarbonylmethyl.

The term "aminosulfonyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of aminosulfonyl include, but are not limited to, aminosulfonyl, dimethylaminosulfonyl, and ethylmethylaminosulfonyl.

The term "carbonyl," as used herein, refers to a -C(O)- group.

The term "carboxy," as used herein, refers to a $-CO_2H$ group.

The term "carboxyalkyl," as used herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of carboxyalkyl include, but are not limited to, carboxymethyl, 2-carboxyethyl, and 3-carboxypropyl.

The term "cyano," as used herein, refers to a -CN group.

The term "cyanoalkyl," as used herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cyanoalkyl include, but are not limited to, cyanomethyl, 2-cyanoethyl, and 3-cyanopropyl.

The term "formyl," as used herein, refers to a -C(O)H group.

The term "formylalkyl," as used herein, refers to a formyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of formylalkyl include, but are not limited to, formylmethyl and 2-formylethyl.

The term "halo" or "halogen," as used herein, refers to -Cl, -Br, -I or -F.

The term "haloalkoxy," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, and pentafluoroethoxy.

The term "haloalkyl," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3-fluoropentyl.

The term "hydroxy," as used herein, refers to an -OH group.

The term "hydroxyalkyl," as used herein, refers to a hydroxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, and 3-hydroxypropyl.

The term "mercapto," as used herein, refers to a -SH group.

The term "mercaptoalkyl," as used herein, refers to a mercapto group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of mercaptoalkyl include, but are not limited to, 2-mercaptoethyl and 3-mercaptopropyl.

The term "N-protecting group" or "nitrogen-protecting group," as used herein, refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures. N-protecting groups comprise carbamates, amides, alkyl derivatives, amino acetal derivatives, N-benzyl derivatives, imine derivatives, enamine derivatives, and N-heteroatom derivatives. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, phenylsulfonyl, benzyl, triphenylmethyl (trityl), t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz). Commonly used N-protecting groups are disclosed in T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991).

The term "nitro," as used herein, refers to a $-NO_2$ group.

The term "oxy," as used herein, refers to a -O- moiety.

The term "sulfonyl," as used herein, refers to a $-SO_2-$ group.

The term "thio," as used herein, refers to a -S- moiety.

Compounds of the present invention can exist as stereoisomers, wherein asymmetric or chiral centers are present. Stereoisomers are designated "R" or "S," depending on the configuration of substituents around the chiral carbon atom. The terms "R" and "S" used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem., (1976), 45: 13-30. In particular, the stereochemistry at the two bridgehead carbon atoms, shown in Formula (I), may independently be either (R) or (S), unless specifically noted otherwise. The present invention contemplates various stereoisomers and mixtures thereof and are specifically included within the scope of this invention. Stereoisomers include enantiomers, diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of

ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts are well-known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 et seq. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid and such organic acids as acetic

acid, fumaric acid, maleic acid, 4-methylbenzenesulfonic acid, succinic acid and citric acid.

Basic addition salts can be prepared in situ during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

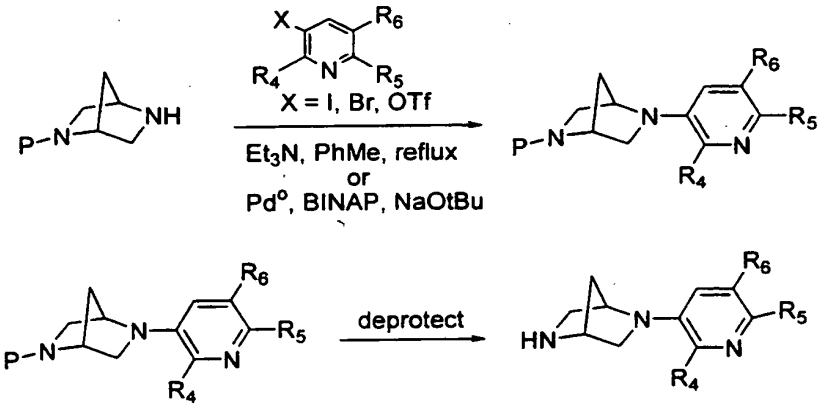
Abbreviations

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are: Ac for acetyl; AcOH for acetic acid; BINAP for 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Boc for tert-butoxycarbonyl; $(Boc)_2O$ for di-tert-butyl dicarbonate; dba for dibenzylideneacetone; DMF for N,N-dimethylformamide; dppf for 1,1'-bis(diphenylphosphino)ferrocene; EtOAc for ethyl acetate; Et_2O for diethyl ether; EtOH for ethanol; eq for equivalents; formalin for a solution of formaldehyde (37% by weight) in water; HPLC for high pressure liquid chromatography; LAH for lithium aluminum hydride; MeOH for methanol; Tf for SO_2CF_3: TFA for trifluoroacetic acid; THF for tetrahydrofuran; TMS for trimethylsilyl; and TsOH for para-toluenesulfonic acid monohydrate.

Preparation of Compounds of the Present Invention

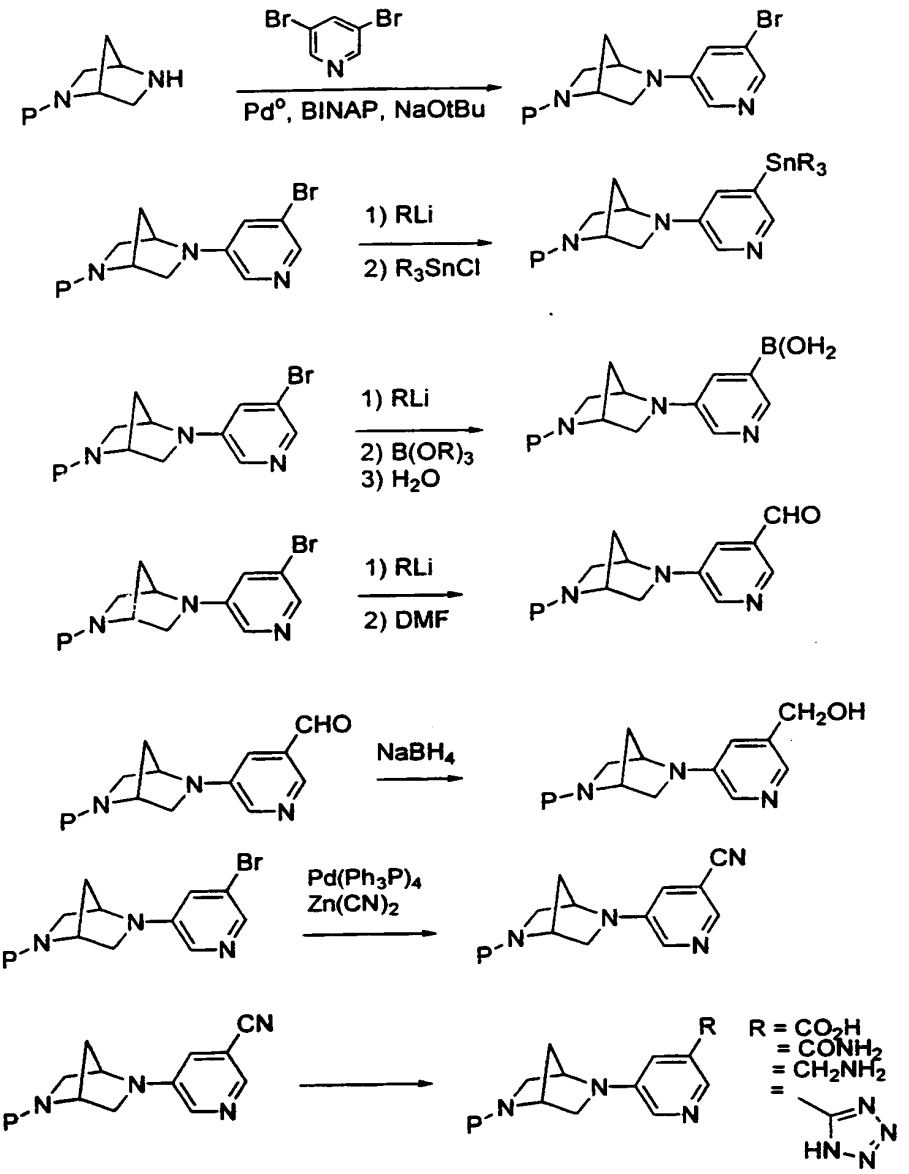
The compounds and processes of the present invention will be better understood in connection with the following synthetic Schemes and methods which illustrate a means by which the compounds of the present invention can be prepared.

Scheme 1



The compounds of the present invention can be prepared according to the general approach outlined in Scheme 1. Suitably protected bicyclic diamines, as shown in Scheme 1 wherein P is a nitrogen-protecting group such as alkyl, benzyl, or Boc, can be coupled with a halogenated heterocycle, wherein R_4, R_5, and R_6 are as defined in formula I, in the presence of an amine base. Alternatively, less-reactive heterocycles can be coupled using the procedures described in (Wagaw, S. and Buchwald, S. L., J. Org. Chem. 1996, 61, 7240-7241; Bryant, H.Y. and Buchwald, S.L., Journal of Organometallic Chemistry (1999) 576, 125-146). Deprotection under standard conditions affords the desired compounds. Diazabicycloheptanes may be prepared as generally taught and described in Examples 1, 2, 15, and 16. Diazabicyclooctanes may be prepared as generally taught and described in Examples 10, 35, 42, 49, 59, and 60. Diazabicyclononanes may be prepared as generally taught and described in Examples 36, 56, and 57. One skilled in the art would understand that the preparation of larger diazabicyclo compounds, for example decanes, etc., may be prepared synthetically by the Schemes and Examples contained herein as well as general synthetic methodology.

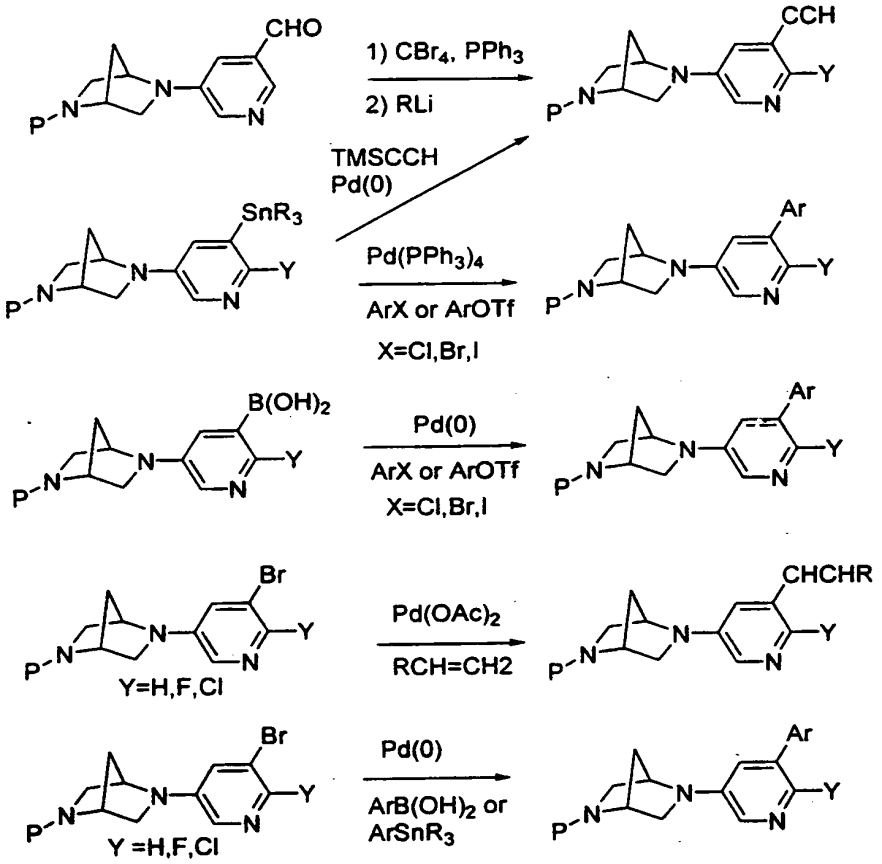
Scheme 2



The transformations outlined in Scheme 2 provide compounds which can in turn be elaborated to provide other 5-substituted pyridines. For example, complete or partial hydrolysis of the nitrile leads to the carboxylic acid and amide, respectively. Reduction of the nitrile affords the amine, while cyclization with $TMSN_3$ in the presence of Bu_2O as described in (Wittenberger and Donner, J. Org. Chem. 1993 58, 4139) provides the tetrazolyl derivative. The aldehyde can be converted to oximes and hydrazones or

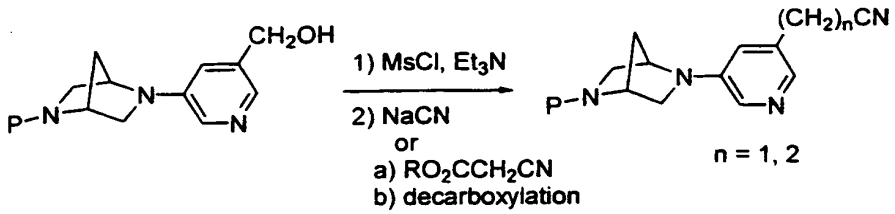
subjected to reductive amination conditions to provide a variety of substituted aminomethyl compounds. Grignard reactions on the aldehyde provides a route to a variety of substituted hydroxymethyl analogs.

Scheme 3



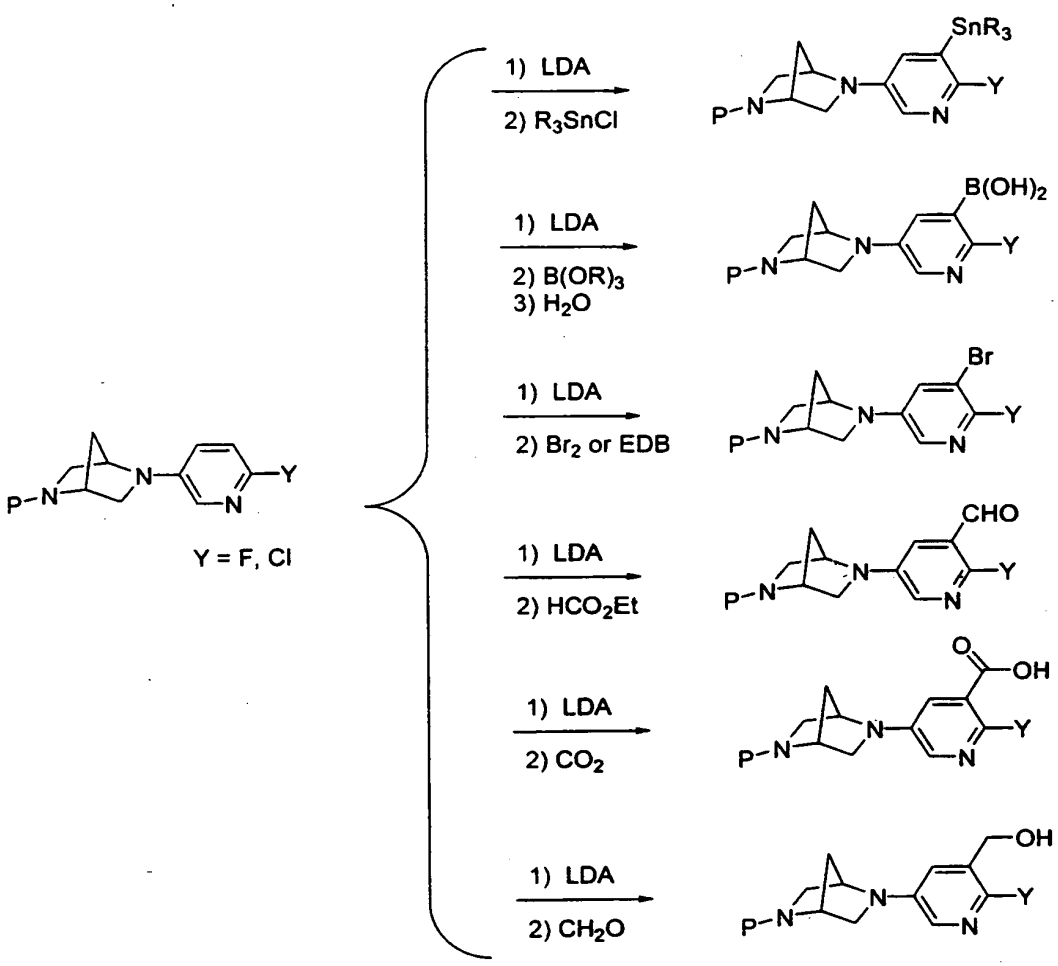
Aldehydes, as shown in Scheme 3, can be elaborated to terminal alkynes using the procedure described in (Tetrahedron Lett. (1972), 3769-3772). Additional elaborations are possible from the tin and boronic acid derivatives, from Scheme 2, which can be coupled with a variety of aryl and vinyl halides and sulfonate esters using transition metal catalysis (e.g., Stille and Suzuki couplings). The 5-bromo derivatives can be engaged in a variety of Pd-catalyzed couplings with alkenes and alkynes (Heck couplings), aryl and vinylstannanes and boronic acids (Stille and Suzuki couplings), as well as alkoxycarbonylations.

Scheme 4



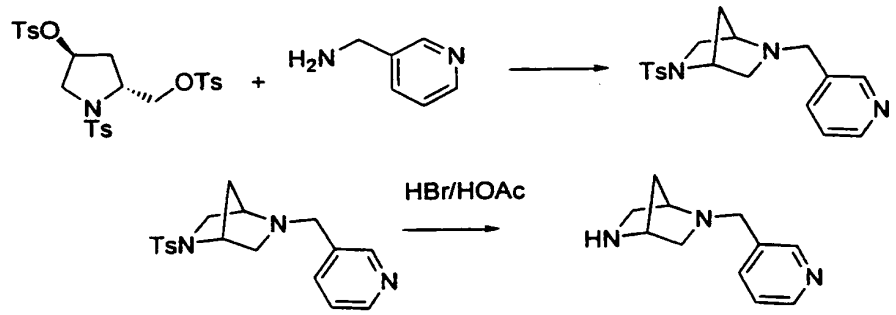
Chain extensions (CN displacement, malonic ester synthesis) can be carried out as described in Scheme 4 to provide the range of substitution patterns encompassed in the claims.

Scheme 5



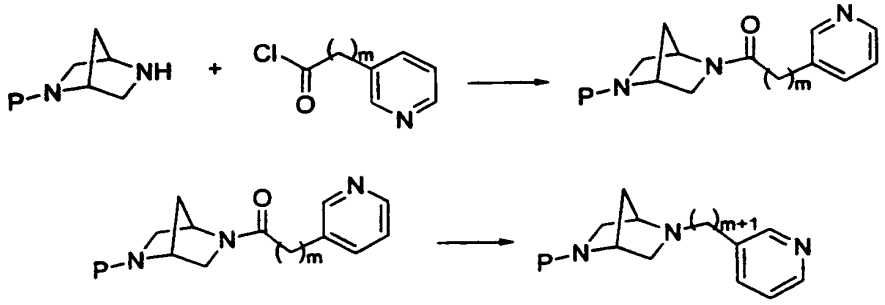
In the cases where the 6-position of the heterocycle is substituted with halogen, an alternate method for functionalizing the 5-position involves ortho-directed metalation according to (Gribble et al., Tetrahedron Lett. (1980) 21, 4137). The metalated species can be trapped with various electrophiles, as exemplified in Scheme 5, to afford intermediates which can be further elaborated as described in Schemes 3 and 4.

Scheme 6



Compounds with 1-5 methylenes between the aromatic heterocycle and the diazabicyclic ring system can be prepared according to the procedure described in Scheme 6. Aminoalkyl heterocycles, prepared using standard synthetic chemistry methodology or purchased commercially, can be condensed with monocyclic precursors to provide N-substituted diazabicyclic systems. For example, (3S,5R)-1-[(4-methylphenyl)sulfonyl]-3-[(4-methylphenyl)sulfonyloxy]-5-[(4-methylphenyl)sulfonyloxymethyl]pyrrolidine prepared as described in (J. Med. Chem., (1990) 33, 1344), can be condensed with an aminoalkylheterocycle to provide an N-substituted[2.2.1]diazabicyclic system which upon removal of the protecting group, for example with HBr/HOAc, provides the desired compounds. Other spacer lengths are possible by straightforward variation of the starting aminoalkyl heterocycle.

Scheme 7



Scheme 7 describes an alternate method of preparing compounds with 1-5 methylenes between the aromatic heterocycle and the diazabicyclic ring system. Mono-protected diazabicyclic systems can be acylated with appropriate heterocyclic acid chlorides or anhydrides followed by reduction of the resultant amides using standard

methods available to one skilled in the art provides the desired chain extended compounds.

The following examples are presented to describe preferred embodiments and utilities of the invention and are not meant to limit the invention unless otherwise stated in the claims appended hereto.

Example 1

(1S,4S)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 1A

tert-butyl (1S,4S)-5-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

In a dry, nitrogen-purged flask, tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (330 mg, 1.6 mmol), prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), in anhydrous toluene (6 mL) was treated with 2-chloro-5-iodopyridine (383 mg, 1.6 mmol), available as described in (Tetrahedron Lett., (1993), 34, 7493-7496), $Pd_2(dba)_3$ (156 mg, 0.16 mmol), BINAP (212 mg, 0.34 mmol), and sodium tert-butoxide (230 mg, 2.4 mmol). The mixture was heated at 70 °C for 24 hours. The reaction mixture was poured into diethyl ether (10 mL) and washed successively with 1N HCl, saturated $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on SiO_2, eluting with ethyl acetate:hexanes (1:1) to provide the title compound (300 mg, 58% yield) as a light brown solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41(s, 4.5H), 1.46(s, 4.5H), 1.93-2.05(m, 2H), 3.14 (d, J=14.7 Hz, 0.5H), 3.35(d, J=14.7 Hz, 0.5H), 3.42(m, 2H), 3.57 (d, 8.45 Hz, 1H), 4.37(s, 1H), 4.53(s, 0.5H), 4.65(s, 0.5H), 6.82(dd, J=2.94, 8.83 Hz, 1H), 7.13(d, J=8.46 Hz, 1H), 7.71(s, 1H); MS (DCI/NH_3) m/z 310 $(M+H)^+$.

Example 1B

(1S,4S)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 1A, tert-butyl (1S,4S)-5-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (386 mg, 1.25 mmol), was charged to a dry, nitrogen-purged flask, and anhydrous ethanol (12 mL) was added. The solution was cooled to 0 °C and treated with 4N HCl/dioxane (1.3 mL). The mixture was allowed to warm to ambient temperature over 0.5 hours, the solvent was removed under reduced pressure, and the residue purified on SiO_2, eluting with 10% MeOH/CH_2Cl_2/1% NH_4OH to afford the title compound (202 mg, 77% yield) as the free base. The free base was combined with p-toluenesulfonic acid (1 eq) and recrystallized from ethanol/ethyl acetate to provide the title compound. ^{1}H NMR(free base, $CDCl_3$, 300 MHz) δ 1.91-2.13 (AB quartet, J=17.6, 40.7 Hz, 2H), 3.03 (d, J=11.3Hz, 1H), 3.19 (s, 2H), 3.63 (dd, J=2.0, 11.3 Hz, 1H), 3.89 (s, 1H), 4.30 (s, 1H), 6.80 (dd, J=3.4, 8.9 Hz, 1H), 7.20 (d, J=8.8 Hz, 1H), 7.72 (d, J=3.3 Hz, 1H); MS(DCI/NH_3) m/z 210 $(M+H)^+$, 227 $(M+NH_4)^+$; Anal. calculated for $C_{10}H_{12}N_3Cl$•1.25 TsOH C,52.92; H,5.21; N, 9.69. Found C,52.92; H, 5.35; N, 9.64.

Example 2

(1S,4S)-2-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 2A

tert-butyl (1S,4S)-5-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (342 mg, 1.7 mmol), prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), in anhydrous toluene (8.5 mL) was treated with 3,6-dichloropyridazine (256 mg, 1.7 mmol, Aldrich Chemical Company) and triethylamine (0.24 mL, 170 mg, 1.7 mmol). The reaction mixture was heated to reflux for 16 hours, concentrated under reduced pressure, and the residue purified on SiO_2 (5%MeOH/CH_2Cl_2/1%NH_4OH) to provide the title compound (432 mg, 81% yield) as a white solid. ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.42(s, 4.5H), 1.46(s, 4.5H), 1.91-2.05(m, 2H), 3.36-3.46 (m, 3H), 3.54-3.60 (m, 1H), 4.57(s, 0.5H),

4.70(s, 0.5H), 4.92(s, 0.5H), 5.07(s, 0.5H), 6.59(d, J=9.20 Hz, 1H), 7.34(d, J=9.56 Hz, 1H); MS (DCI/NH_3) m/z 311 $(M+H)^+$, 328 $(M+NH_4)^+$.

Example 2B

(1S,4S)-2-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product from Example 2A (432 mg, 1.4 mmol) in EtOH (14 mL) at 0 °C was treated with 4M HCl/dioxane (1.4 mL). The reaction was allowed to warm to ambient temperature, concentrated under reduced pressure, and the residue was purified on SiO_2 (10%MeOH/CH_2Cl_2/1%NH_4OH) to provide the free base (231 mg, 79% yield). The free base was treated with p-toluenesulfonic acid (3 eq), and the resultant salt was recrystallized from ethanol/ethyl acetate. ^1H NMR(free base, $CDCl_3$, 300 MHz) δ 2.23 (d, J=11.77 Hz, 1H), 2.38(d, J=11.77 Hz, 1H), 3.54(AB quartet, J=11.77, 24.27 Hz, 2H), 3.90(m, 2H), 4.72(s, 1H), 5.21(s, 1H), 7.72(d, J=9.56 Hz, 1H), 7.87(d, J=9.92 Hz, 1H); MS (DCI/NH_3) m/z 211 $(M+H)^+$, 228 $(M+NH_4)^+$; Anal. calculated for $C_9H_{11}N_4Cl \cdot 2.65$ TsOH•1.05 H_2O, C, 48.24; H, 5.04; N, 8.17. Found C, 48.29; H, 5.38; N, 8.18.

Example 3

(1S,4S)-2-(6-amino-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane trihydrochloride

Example 3A

tert-butyl (1S,4S)-5-(6-nitro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

5-Bromo-2-nitropyridine, prepared as described in (J. Am. Chem. Soc., (1945) 67, 668), and tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), were coupled according to the procedure of Example 2A to provide the title compound.

Example 3B

(1S,4S)-2-(6-amino-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane trihydrochloride

The product from Example 3A in methanol:ethanol (1:1) was treated with 10% Pd/C under a hydrogen atmosphere (1 atm) for 14 hours. The mixture was filtered, concentrated, and the residue treated with HCl/ether to provide the title compound (65% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.00 (m, 2H), 3.00 (br s , 2H), 3.4-3.5 (m, 2H), 4.40 (s, 1H), 4.60 (s,1H), 7.00 (d, J=6.3 Hz, 1H), 7.30 (s, 1H), 7.50 (br s, 2H, exchangeable), 7.70 (d, J=6.3 Hz, 1H), 9.40 (br s, 1H, exchangeable), 9.80 (br s, 2H, exchangeable), 13.0 (br s, 1H, exchangeable).

Example 4

(1S,4S)-2-(6-chloro-5-methyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 4A

tert-butyl (1S,4S)-5-(6-chloro-5-methyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

3,6-Dichloro-4-methylpyridazine (Aldrich Chemical Company) and tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), were processed as described in Example 2A to provide the title compound (56% yield). ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.41 (s, 4.5H), 1.43 (s, 4.5H), 1.90-2.09 (m, 2H), 2.31(s, 3H), 3.35-3.45 (m, 3H), 3.53-3.60(m, 1H), 4.56(s, 0.5H), 4.69(s, 0.5H), 4.90(s, 0.5H), 5.08(s, 0.5H), 6.48(s, 1H); MS (DCI/NH_3) m/z 325 $(M+H)^+$.

Example 4B

(1S,4S)-2-(6-chloro-5-methyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product of Example 4A was processed as described in Example 2B to provide the title compound (81% yield). ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.84 (d, J=10.29 Hz, 1H), 1.96 (d, J=9.93 Hz,1H), 2.32 (s, 3H), 2.92-3.02 (m, 2H), 3.36 (s, 1H), 3.58 (dd, J=2.21, 9.56 Hz, 1H), 3.83 (s, 1H), 4.76-4.88 (m, 1H), 6.94 (s, 1H); MS (DCI/NH_3) m/z

225 $(M+H)^+$, 242 $(M+NH_4)^+$; Anal. calculated for $C_{10}H_{13}N_4Cl \cdot 2.0$ TsOH C, 50.63; H, 5.13; N-9.70. Found C, 50.32; H, 5.15; N, 9.82.

Example 5

(1S,4S)-2-(6-chloro-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 2B (1.0 eq) in formalin (0.1 M) was treated with $NaCNBH_3$ (1.2 eq) at 0 °C. The reaction was allowed to warm to ambient temperature and stirred for 12 hours. The reaction mixture was quenched with saturated aqueous K_2CO_3, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on SiO_2 (10%MeOH/CH_2Cl_2/1%NH_4OH) to provide the free base as a colorless oil (87% yield). The free base was treated with p-toluenesulfonic acid (1.5 eq) and the resultant salt was recrystallized from ethanol/ethyl acetate to provide the title compound. ^{1}H NMR(free base, CD_3OD, 300 MHz) δ 2.33 (d, J=10.30 Hz, 1H), 2.48 (s, 3H), 2.50 (d,J=11.77 Hz, 1H), 2.98-3.01 (m, 1H), 3.71-3.87 (m, 3H), 4.49 (s, 1H), 5.06 (s, 1H), 7.54 (d, J=10.26 Hz, 1H), 7.78 (d, J=8.09 Hz, 1H); MS (DCI/NH_3) m/z 225 $(M+H)^+$, 242 $(M+NH_4)^+$; Anal. calculated for $C_{10}H_{13}N_4Cl \cdot 0.95$ TsOH$\cdot 0.60$ H_2O: C, 50.11; H, 5.51; N, 14.04. Found C, 50.21; H, 5.76; N, 13.98.

Example 6

(1S,4S)-2-(6-chloro-5-methyl-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product from Example 4B was processed as described in Example 5 to provide the title compound (39% yield). ^{1}H NMR (CD_3OD, 300 MHz) δ 1.89 (d, J=9.93 Hz, 1H), 2.05 (d, J=9.93 Hz, 1H), 2.29 (s, 3H), 2.45 (s, 3H), 2.76 (d, J=9.56 Hz, 1H), 2.97 (dd, J=1.83, 5.14 Hz, 1H), 3.39 (dd, J=2.21, 9.56 Hz,1H), 3.58-3.68 (m, 2H), 4.80 (br s, 1H), 6.48 (s, 1H); MS (DCI/NH_3) m/z 239 $(M+H)^+$, 256 $(M+NH_4)^+$; Anal. calculated for $C_{11}H_{15}N_4Cl \cdot 2.2$ TsOH$\cdot 1.80$ H_2O: C, 48.65; H, 5.62; N, 8.48. Found C, 48.61; H, 5.50; N, 8.53.

Example 7

(1S,4S)-2-(4-chloro-1-phthalazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 7A

tert-butyl (1S,4S)-5-(4-chloro-1-phthalazinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

1,4-Dichlorophthalazine (Aldrich Chemical Company) and tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), were processed as described in Example 2A to provide the title compound (62% yield). ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.44 (s, 4.5H), 1.47 (s, 4.5H), 1.95-2.08 (m, 2H), 3.46-3.58 (m, 1H), 3.64 (d, J=8.47 Hz, 0.5H), 3.75 (d, J=8.81 Hz, 0.5H), 3.91(d, J=10.51 Hz, 1H), 4.19 (dd, J=2.03, 6.78 Hz, 1H), 4.59(br s, 0.5H), 4.69 (br s, 0.5H), 5.15 (s, 1H), 7.26-7.81 (m, 2H), 8.04-8.12 (m, 1H), 8.21 (dd, J=1.70, 7.80 Hz, 1H); MS (DCI/NH_3) m/z 361$(M+H)^+$.

Example 7B

(1S,4S)-2-(4-chloro-1-phthalazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product of Example 7A was processed according to the procedure described in Example 2B to provide the title compound (83% yield). ^{1}H NMR(free base, $CDCl_3$, 300 MHz) δ 1.91 (d, J=9.93 Hz, 1H), 2.05(d, J=9.93 Hz, 1H), 3.22 (dd, J=1.84, 8.45 Hz, 1H), 3.55-3.70 (m, 2H), 3.95 (s, 1H), 4.21 (dd, J=2.21, 9.19 Hz, 1H), 5.07 (s, 1H), 7.76-7.94 (m, 2H), 8.06 (d, J=8.09 Hz, 1H), 8.15 (d, J=9.56 Hz, 1H); MS (DCI/NH_3) m/z 261$(M+H)^+$; Anal. calculated for $C_{13}H_{13}N_4Cl$•2.105 TsOH•0.25 H_2O: C, 53.08; H, 4.87; N, 8.94. Found C, 53.14; H, 5.24; N, 8.87.

Example 8

(1S,4S)-2-(4-chloro-1-phthalazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product of Example 7B was processed according to the procedure described in Example 5 to provide the title compound (53% yield). ^{1}H NMR free base (CD_3OD,

300 MHz) δ 2.34 (s, 3H), 2.54 (d, J=8.47 Hz, 1H), 2.68 (d, J=10.51 Hz, 1H), 3.48 (d, J=11.19 Hz, 1H), 4.28-4.45 (m, 2H), 4.59-4.66 (m, 2H), 5.34 (s, 1H), 8.08-8.15 (m, 1H), 8.23 (t, J=7.80 Hz, 1H), 8.38-8.46 (m, 2H); MS (DCI/NH_3) m/z 275 $(M+H)^+$; Anal. calculated for $C_{14}H_{15}N_4Cl \cdot 2.0$ TsOH: C, 54.52; H, 5.50; N, 9.05. Found C, 54.18; H, 4.98; N, 9.08.

Example 9

(1S,4S)-2-(6-chloro-5-methoxycarbonyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 9A

tert-butyl (1S,4S)-5-[6-chloro-5-(methoxycarbonyl)-3-pyridazinyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

Methyl 3,6-dichloropyridazine-4-carboxylate and tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), were processed as described in Example 2A to provide the title compound (41% yield). ^1H NMR($CDCl_3$, 300 MHz) δ 1.42 (s, 4.5H), 1.47 (s, 4.5H), 1.90-2.11 (m, 2H), 2.86 (d, J=9.93 Hz, 1H), 3.40-3.62 (m, 2H), 3.72 (d, J=9.90 Hz, 1H), 3.93 (s, 3H), 3.51 (s, 0.5H), 4.63 (s, 0.5H), 5.05-5.15 (m, 1H), 7.49 (s, 1H); MS (DCI/NH_3) m/z 368 $(M+H)^+$.

Example 9B

(1S,4S)-2-(6-chloro-5-methoxycarbonyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product from Example 9A was processed according to the procedure described in Example 2B to provide the title compound (73% yield). ^1H NMR($CDCl_3$, 300 MHz) δ 1.88 (d, J=10.29 Hz, 1H), 2.01 (d, J=9.92 Hz, 1H), 2.81 (d, J=9.92 Hz, 1H), 3.13-3.27 (m, 2H), 3.76 (dd, J=2.21, 9.93 Hz, 1H), 3.87 (s, 1H), 3.93 (s, 3H), 5.00 (s, 1H), 7.48 (s, 1H); MS (DCI/NH_3) m/z 269 $(M+H)^+$; Anal. calculated for $C_{11}H_{13}N_4O_2Cl \cdot 2.5$ TsOH$\cdot 1.1$ H_2O: C, 47.61; H, 4.93; N, 7.79. Found C, 47.61; H, 5.07; N, 7.75.

Example 10

3-(6-nitro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane dihydrochloride

Example 10A

tert-butyl 3-(6-nitro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

tert-Butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (0.4 g; 1.9 mmol), prepared as described in (J. Med. Chem., (1998) 41, 674), 5-bromo-2-nitropyridine (0.43 g; 2.27 mmol), prepared as described in (J. Am. Chem. Soc., (1945) 67, 668), and triethylamine (0.23 g; 2.27 mmol) in toluene (10 mL) were heated at reflux for 14 hours. After evaporation of the solvent, additional triethylamine (0.23 g) was added and the mixture further heated at 140 °C for 2 hours. The residue was purified on SiO_2 (CH_2Cl_2:EtOAc 9:1) to provide the title compound.

Example 10B

3-(6-nitro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane dihydrochloride

The product from Example 10A was treated with 1M HCl/ether to provide the title compound (55% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.9-2.0 (m, 4H), 3.4-3.5 (m, 2H), 4.00 (d, J=11 Hz, 2H), 4.20 (br s, 2H), 7.5-7.6 (m, 1H), 8.2-8.3 (m, 2H), 9.6-9.7 (br s, 3H, exchangeable).

Example 11

3-(6-amino-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane trihydrochloride

Example 11A

tert-butyl 3-(6-amino-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

The product from Example 10A (200 mg) was treated with 10% Pd/C (20 mg) in a 1:1 mixture of methanol:ethanol (5 mL) under a hydrogen atmosphere (1 atm). After

filtration to remove the catalyst, the filtrate was concentrated and the residue triturated with diethyl ether to afford the the title compound as a violet solid.

Example 11B

3-(6-amino-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane trihydrochloride

The product from Example 11A was treated with 1M HCl/ether to provide the title compound (72% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.00 (s, 4H), 3.2 (d, J=11 Hz, 2H), 3.4 (s, J=11 Hz, 2H), 4.20 (br s, 2H), 5.80 (s, 2H, exchangeable), 7.00, (d, J=8.5 Hz, 1H), 7.40 (br s, 1H), 7.80 (br s, 2H, exchangeable), 7.9-8.0 (m, 1H), 9.10 (br s, 2H, exchangeable).

Example 12

3-(6-chloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane dihydrochloride

The product from Example 11A (0.03 g; 0.103 mmol) in 12M HCl (0.13 mL) was treated with sodium nitrite (10 mg, 0.129 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stir overnight. The mixture was neutralized by addition of $NaHCO_3$ and then extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified on SiO_2 (10% MeOH/CH_2Cl_2/1% NH_4OH) to provide the free base. The free base was treated with 1M HCl/ether to provide the title compound (43% yield). ^{1}H NMR free base ($CDCl_3$, 300 MHz) δ 1.8 (m, 4H), 2.1 (br s, 1H, exchangeable), 3.0 (d.K=11Hz, 2H), 3.4-3.7 (br s, 2H), 7.0-7.2 (m, 2H0, 7.9 (m, 1H).

Example 13

3-(3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane dihydrochloride

The product from Example 12 was processed as described in Example 11A. The crude product was purified on SiO_2 (10% MeOH/CH_2Cl_2/1% NH_4OH) and then treated with 1M HCl/ether to provide the title compound (40 % yield). ^{1}H NMR (DMSO-d_6, 300

MHz) δ 2.20 (br s, 4H), 3.5 (d, J=11 Hz, 2H), 4.00 (d, J=11 Hz, 2H), 4.4 (br s, 1H), 7.9-8.0 (m, 1H), 8.2-8.3 (m, 2H), 8.5 (d, J=3.6 Hz, 1H); MS (DCI/NH_3) m/z 190 $(M+H)^+$.

Example 14

3-(3-pyridazinyl)-3.8-diazabicyclo[3.2.1]octane dihydrochloride

3-(6-Chloro-3-pyridazinyl)-3,8-diazabicyclo[3.2.1]octane, prepared as described in (J. Med. Chem., (1998) 41, 674) was hydrogenated according to the procedure described in Example 11A. The crude product was purified on SiO_2 (10% MeOH/CH_2Cl_2/1% NH_4OH) and treated with 1M HCl/ether to afford the title compound (40 % yield). ^1H NMR (free base, $CDCl_3$, 300 MHz) δ 1.9-2.0 (m, 5H), 3.1 (d, J=11 Hz, 2H), 3.70 (br s, 2H), 4.0 (d, J=11 Hz, 2H), 6.8 (d, J=8.8 Hz, 1H), 7.2 (dd, J=8.8, 3.8 Hz, 1H), 8.6 (d, J=3.6 Hz, 1H); MS (DCI/NH_3) m/z 191 $(M+H)^+$.

Example 15

(1R,4R)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 15A

tert-butyl (1R,4R)-5-benzyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

(1R,4R)-2-(benzyl)-2,5-diazabicylo[2.2.1]heptane dihydrobromide (12.4 g, 35.5 mmol), prepared as described in (J. Med. Chem., (1990) 33, 1344) and K_2CO_3 (16.2 g, 117 mmol) in 100 mL of DMF were treated with di-tert-butyl dicarbonate (8.1 g, 37 mmol) at ambient temperature. After stirring for 16 hours, the mixture was filtered and the filtrate diluted with water (500 mL). The mixture was extracted with Et_2O (3x300 mL). The extracts were combined, washed with 50% brine (10x20 mL), dried over $MgSO_4$, and the solvent removed under reduced pressure to provide the title compound (9.7 g, 94%). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.62 (m, 1H), 1.79 (d, J=9.2 Hz, 1H), 2.51 (m, 1H), 2.75 (m, 1H) 3.07 (t, J=10.2 Hz, 1H), 3.32-3.41 (m, 2H), 3.67 (s, 1H), 4.16 (d, 9.8 Hz, 1H), 7.19-7.33 (m, 5H); MS (DCI/NH_3) m/z 199 $(M+H)^+$, 216 $(M+NH_4)^+$.

Example 15B

tert-butyl (1R,4R)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15A (2 g, 6.9 mmol) in 50 mL of EtOH was treated with 10% Pd/C (150 mg) under an H_2 atmosphere (1 atm) for 16 hours. The mixture was filtered and the solvent was evaporated under reduced pressure to yield 1.28 g (93.4 %) of the title compound. ^{1}H NMR (DMSO-d_6, MHz) δ 1.39 (s, 9H), 1.54 (d, J=5.6 Hz, 1H), 1.58 (t, J=9.5 Hz, H), 2.70-2.81 (M, 2H), 3.50 (dd, J=1.02, 10.50. 1H), 3.17 (m, 1H), 3.50 (s, 1H), 4.17 (d, J=10.17 Hz, H); MS (DCI/NH_3) m/z 199 $(M+H)^+$, 216 $(M+NH_4)^+$.

Example 15C

tert-butyl (1R,4R)-5-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B (0.5 g, 2.5 mmole), 2-chloro-5-iodopyridine (0.88 g, 3.35 mmole, available as described in Tetrahedron Lett., 1993, 34, 7493-7496), $Pd_2(dba)_3$ (0.13 g, 0.16 mmole), BINAP (0.22 g, 0.34 mmole), and sodium tert-butoxide (0.325 g, 3.57 mmole) in anhydrous toluene (10 mL) were heated to 70 °C for16 hours. The mixture was filtered, concentrated under reduced pressure, and the residue purified by chromatography (silica gel; hexane:EtOAc, 9:1 to 1:1) to provide the title compound (0.522 g, 67 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.33-1.38 (m 9H), 2.50 (br s, 2H), 3.02 (m, 1H), 3.16 (d, J=10.17 Hz, 1H), 3.27 (m, 1H), 3.53 (m, 1H), 4.43 (m, 1H), 4.58 (br, s 1H), 7.11 (dd, J=3.05, 8.81 Hz, 1H), 7.24 (d, J=27.46 Hz, 1H), 7.77 (d, J=3.05Hz, 1H); MS (DCI/NH_3) m/z 310 $(M+H)^+$.

Example 15D

(1R,4R)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product of Example 15C (478 mg, 1.5 mmole) in CH_2Cl_2 (3 mL) was treated with trifluoroacetic acid (3 mL). After stirring for one hour at ambient temperature, the solvent was removed and the residue dissolved in saturated Na_2CO_3 (20 mL). The mixture was extracted with EtOAc (4 X 20mL), dried over $MgSO_4$, concentrated under reduced pressure, and the residue purified (SiO_2; 10% MeOH/$CHCl_3$/1% NH_4OH) to

provide the free base. The free base was treated with TsOH in hot EtOAc to provide the title compound (451 mg, 71%). $[\alpha]_D^{23}$ -8.21 (c 0.21, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.93 (d, J=11.52 Hz, 1H), 2.14 (d J=11.19 Hz 1H), 2.29 (s, 3H), 3.13-3.31 (m, 3H), 3.61 (dd, J=2.37, 10.85, 1H), 4.48 (s, 1H), 4.68 (s, 1H), 7.13 (d, J=8.48 Hz, 2H), 7.17 (dd, J=3.05, 8.62 Hz, 1H), 7.31 (d, J=8.82, 1H), 7.49 (d J=7.66 Hz, 2H), 7.85 (d J=3.39 Hz, 1H); MS (DCI/NH_3) m/z 210 $(M+H)^+$; Anal. Calcd for $C_{10}H_{12}N_3Cl \cdot C_7H_8O_3S$: C, 53.47; H, 5.28; N, 11.00. Found: C, 53.43; H, 5.36; N, 10.97.

Example 16

(1R,4R)-2-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 16A

tert-butyl (1R,4R)-5-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 3,6-dichloropyridazine (purchased from Aldrich Chemical Co.) were processed as described in Example 2A to provide the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.48 (m 9H), 2.93 (br, s 2H), 3.18 (d, J=12.17Hz, 1H), 3.3-3.51 (m, 2H), 3.55 (m, 1H), 4.49 (m, 1H), 4.86 (br, s 1H), 7.12 (m, 1H), 7.51 (d, J=9.49 Hz, 1H); MS (DCI/NH_3) m/z 311 $(M+H)^+$.

Example 16B

(1R,4R)-2-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product from Example 16A (353 mg, 1.1 mmole) and para-toluenesulfonic acid (660 mg 3.5 mmole) in EtOAc (10 mL) were heated at 70 °C for one hour and then cooled to ambient temperature. The obtained solid was washed with EtOAc (2x10 mL), ether (2x10 mL), and dried under reduced pressure to provide the title compound (597 mg, 94.7%). $[\alpha]_D^{23}$ +59.3 (c 1.0, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.96 (d, J=10.51 Hz, 1H), 2.17 (d, J=10.17 Hz 1H), 2.29 (s, 6H), 3.24-3.28 (m, 2H), 3.56-3.67 (m, 2H), 4.53 (s, 1H), 4.95 (s, 1H), 7.11 (d, J=7.79, 4H), 7.21 (d, J=9.41 Hz, 1H), 7.49

(d, J=8.11 Hz, 4H), 7.62 (d, J=9.49 Hz, 1H); MS (DCI/NH_3) m/z 211 $(M+H)^+$; Anal. Calcd for $C_9H_{11}N_4Cl \cdot 2C_7H_8O_3S$: C, 49.77; H, 4.90; N, 10.09. Found: C, 49.77; H, 4.99; N, 9.96.

Example 17

(1S,4S)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 17A

tert-butyl (1S,4S)-5-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in J. Med. Chem., (1988) 31, 1598-1611, and 3-bromopyridine (Aldrich Chemical Company) were processed as described in Example 1A to provide the title compound (99% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 4.5H), 1.48 (s, 4.5H), 1.91-2.03 (m, 2H),3.14 (d, J=14.7 Hz, 0.5H), 3.23 (d, J=14.7 Hz, 0.5H), 3.37-3.48 (m, 2H), 3.60 (d, 8.45 Hz, 1H), 4.41 (s, 1H), 4.53 (s, 0.5H), 4.67 (s, 0.5H), 6.85 (dd, J=2.94, 8.83 Hz, 1H), 7.09-7.21 (m, 1H), 7.95-8.06 (m, 2H); MS (DCI/NH_3) m/z 276 $(M+H)^+$.

Example 17B

(1S,4S)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 17A was processed as described in Example 1B to provide the title compound (65% yield). ^1H NMR ($CDCl_3$, free base, 300 MHz) δ 1.82-1.98 (m, 2H), 3.01 (d, J=12.0 Hz, 1H), 3.08 (s, 2H), 3.67 (dd, J=2.0, 11.5 Hz, 1H), 3.76 (s, 1H), 4.32 (s, 1H), 6.78-6.85 (m, 1H), 7.05-7.13 (m, 1H), 7.82-8.01 (m, 2H); MS (DCI/NH_3) m/z 176 $(M+H)^+$, 193 $(M+NH_4)^+$; Anal. Calcd for $C_{10}H_{13}N_3 \cdot 1.0$ TsOH$\cdot 0.4H_2O$: C, 57.58; H,6.20; N, 11.85. Found C, 57.85; H, 6.33; N, 11.47.

Example 18

(1S,4S)-2-(5-chloro-2-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane dihydrochloride

Example 18A

tert-butyl (1S,4S)-5-(5-chloro-2-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), and commercially available 2,5-dichloropyridine were processed as described in Example 2A to provide the title compound (99% yield).

Example 18B

(1S,4S)-2-(5-chloro-2-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane dihydrochloride

The product from Example 18A was treated with HCl in ether to afford the dihydrochloride salt. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.00(m,2H), 3.2-3.3(m,4H), 4.6-4.8(m,2H) 6.80(d,J=7.4Hz, 1H), 7.8(dd, J=7.5, 3.1Hz, 1H), 8.2(d, J=3.1 Hz, 1H), 9.2 (br. s. 1H), 9.8 (br. s., 1H); MS (DCl/NH_3) m/z 210, 212 $(M+H)^+$.

Example 19

3-(5-chloro-2-pyridinyl)-3,8-diazabicyclo[3.2.1]octane dihydrochloride

Example 19A

tert-butyl 3-(5-chloro-2-pyridinyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

tert-Butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate, prepared as described in (J. Med. Chem., (1998) 41, 674), and 2,5-dichloropyridine were processed as described in Example 10A to provide the title compound.

Example 19B

3-(5-chloro-2-pyridinyl)-3,8-diazabicyclo[3.2.1]octane dihydrochloride

The product from Example 19A was processed as described in Example 10B to provide the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.9-2.0(m, 4H), 3.2 (d,

J=11 Hz, 2H), 4.0-4.2 (m, 4H), 7.0 (d, J=7.1 Hz, 1H), 7.8 (dd, J=7.5, 3.1 Hz, 1H), 8.2 (d, J=3.1 Hz, 1H), 9.4 (br. s. 2H); MS (DCl/NH_3) m/z 224, 226 $(M+H)^+$.

Example 20

(1R,4R)-2-(3-pyridinylmethyl)-2,5-diazabicyclo[2.2.1]heptane trihydrobromide

Example 20A

(1R,4R)-2-[(4-methylphenyl)sulfonyl]-5-(3-pyridinylmethyl)-2,5-diazabicyclo[2.2.1]heptane

((2R,4S)-1-[(4-Methylphenyl)sulfonyl]-4-{[(4-methylphenyl)sulfonyl]oxy}pyrrolidinyl)methyl 4-methylbenzenesulfonate (1.5 g, 2.6 mmol), prepared as described in (J. Med. Chem. (1990) 33, 1344) and 3-(aminomethyl)pyridine (1.0 g, 9.3 mmol) in 20 mL of toluene were heated under reflux for 16 hours. The mixture was cooled, filtered, and the filter cake was washed with 20 mL of toluene. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography (silica gel; hexanes:EtOAc, 9:1 to 1:1) to provide the title compound (410 mg, 46%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.86 (d, J=8.5 Hz, 1H), 1.62 (d, J=9.7 Hz, 1H), 2.42 (s, 3H), 2.44 (m, 1H), 2.66 (dd, J=2.4, 9.5 Hz, 1H), 2.99 (dd, J=2.0, 9.5 Hz, 1H), 3.39-3.48 (m, 2H), 3.62-3.41 (d, J=9.5 Hz, 1H), 4.23 (br s, 1H), 4.35 (t, J=5.1 Hz, 1H), 7.31 (m, 1H), 7.43-7.46 (m, 2H), 7.62 (m, 1H), 7.71-7.74 (m, 2H), 8.31-8.43 (m, 2H).

Example 20B

(1R,4R)-2-(3-pyridinylmethyl)-2,5-diazabicyclo[2.2.1]heptane trihydrobromide

The product from Example 20A (320 mg, 0.9 mmol) in acetic acid (3.4 mL) and 33% HBr/acetic acid (7 mL) was heated to 70 °C for 18 hours. After cooling to ambient temperature, the precipitate was filtered, washed with ether, and dried. The resulting solids were recrystallized from EtOH/EtOAc to provide the title compound (332 mg, 80%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.22 (m, 1H), 2.47 (m, 1H), 3.29-3.48 (m, 2H),

3.35 (m, 1H), 3.69 (m, 1H), 4.19-4.53 (m, 2H), 5.59 (m, 2H), 8.05 (m, 1H), 8.62 (m, 1H), 8.78-8.88 (m, 2H); MS (DCI/NH_3) m/z 190 $(M+H)^+$; Anal. Calcd for $C_{11}H_{15}N_3 \bullet 3.0$ HBr$\bullet$0.1 H_2O: C, 30.46; H, 4.23; N, 9.69. Found: C, 30.83; H, 4.25; N, 9.30.

Example 21

(1S,4S)-2-[5-(benzyloxy)-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 21A

tert-butyl (1S,4S)-5-[5-(benzyloxy)-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611) and 3-(benzyloxy)-5-bromopyridine, prepared as described in (US 5,733,912) were coupled according to the procedure described in Example 1A to provide the title compound. MS (DCI/NH_3) m/z 382 $(M+H)^+$.

Example 21B

(1S,4S)-2-[5-(benzyloxy)-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product of Example 21A was processed as described in Example 2B to provide the title compound. ^1H NMR($CDCl_3$, 300MHz) δ 1.78-2.00(m, 4H), 2.97(d, J=12.0 Hz, 1H), 3.05(s, 2H), 3.62(dd, J=3.0, 10.0 Hz, 1H), 3.81(s, 1H), 4.28(s, 1H), 6.42(dd, J=2.0,8.0 Hz, 1H), 7.31-7.51(m, 5H), 7.65(d, J=3.0Hz, 1H), 7.78(d, J=3.0Hz, 1H); MS (DCI/NH_3) m/z 282 $(M+H)^+$; Anal. calculated for $C_{24}H_{27}N_3O_4S \bullet 0.30$ TsOH$\bullet$0.55 H_2O: C, 60.86; H, 5.97; N, 8.16. Found C, 60.83; H, 6.00; N, 8.12.

Example 22

(1S,4S)-2-[5-hydroxy-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 22A

tert-butyl (1S,4S)-5-(5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 21A (0.50 g, 1.31 mmol) in EtOH (15 mL) was treated with 10%Pd/C (0.02g) under a hydrogen atmosphere (1atm) at 40 °C for 6 hours. The reaction mixture was allowed to cool to ambient temperature and the catalyst was removed by filtration. The filtrate was diluted with diethyl ether (125 mL), washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (5%MeOH/CH_2Cl_2) to provide the title compound (0.345 g, 90% yield) as a yellow oil. MS(DCI/NH_3) m/z 292 $(M+H)^+$.

Example 22B

(1S,4S)-2-[5-hydroxy-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 22A was processed as described in Example 2B to provide the title compound. ^1H NMR (MeOD, 300 MHz) δ 2.07 (d, J=12.0 Hz, 1H), 2.28(d, J=13.0 Hz, 1H), 3.32-3.42 (m, 3H), 3.71 (dd, J=4.0, 10.0 Hz, 1H), 4.51 (s, 1H), 4.68 (s, 1H), 6.62 (t, J=2.0 Hz, 1H), 7.51-7.56 (m, 2H); MS (DCI/NH_3) m/z 192 $(M+H)^+$; Anal. calculated for $C_{17}H_{21}N_3O_4S$•0.55 TsOH•2.35 H_2O: C, 50.04; H, 6.06; N, 8.40. Found C, 50.09, H, 6.35; N, 8.38.

Example 23

(1S,4S)-2-(6-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 23A

tert-butyl (1S,4S)-5-(6-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), and 5-bromo-2-methyl-pyridine (purchased from Emka Chemie) were coupled according to the procedure described in Example 1A to provide the title product. MS (DCI/NH_3) m/z 290 $(M+H)^+$.

Example 23B

(1S,4S)-2-(6-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 23A was processed as described in Example 2B to provide the title compound. ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.84 (d, J=9.0Hz, 1H), 1.93 (d, J=9.0Hz, 1H), 2.42 (s, 3H), 2.92 (d, J=7.0Hz, 1H), 3.03-3.10 (m, 2H), 3.65 (dd, J=2.0, 6.0 Hz, 1H), 3.78 (s, 1H), 4.28 (s, 1H), 6.78 (dd, J=4.0, 7.0 Hz, 1H), 6.97 (d, J=4.0 Hz,1H), 7.85 (d, J=2.0 Hz, 1H); MS (DCI/NH_3) m/z 190 $(M+H)^+$; Anal. calculated for $C_{18}H_{23}N_3O_3S$•0.5 TsOH•0.5 H_2O: C, 56.56; H, 6.18; N, 9.20. Found C, 56.57; H, 6.03; N, 9.28.

Example 24

(1R,4R)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 24A

tert-butyl (1R,4R)-5-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 3-bromopyridine (available from Aldrich Chemical Co.) were coupled according to the procedure described in Example 15C to provide the title compound. MS (DCI/NH_3) m/z 276 $(M+H)^+$.

Example 24B

(1R,4R)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 24A was processed as described in Example 2B to provide the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90 (dd, J=12.0, 30.0 Hz, 2H), 2.98 (d, J=9.0 Hz, 1H), 3.08 (s, 2H), 3.63 (dd, J=3.0, 10.0 Hz, 1H), 3.82 (s, 1H), 4.32 (s, 1H), 6.78-6.84 (m, 1H), 7.08-7.15 (m, 1H), 7.95 (dd, 2.0,8.0 Hz, 1H), 8.00 (d, J=3.0Hz, 1H); MS (DCI/NH_3) m/z 176 $(M+H)^+$; Anal. calculated for $C_{17}H_{21}N_3O_3S$•0.45 H_2O: C, 57.43; H, 6.21; N, 11.82. Found C, 57.64; H, 6.11; N, 11.43.

Example 25

(1R,4R)-2-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane

4-methylbenzenesulfonate

Example 25A

tert-butyl (1R,4R)-5-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 16A was process according to the procedure described in Example 29A to provide the title compound. MS (DCI/NH_3) m/z 277 $(M+H)^+$.

Example 25B

(1R,4R)-2-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane

4-methylbenzenesulfonate

The product from Example 25A was processed as described in Example 2B to provide the title compound. ^{1}H NMR (MeOH, 300 MHz) δ 2.11(d, J=12.0 Hz, 1H), 2.26-2.39(m, 3H), 3.65-3.82 (m, 2H), 4.60 (s, 1H), 5.09 (s, 1H), 7.30 (dd, J=1.0, 9.0 Hz, 1H), 7.57-7.65(m, 1H), 8.56 (dd, J=1.0,6.0 Hz, 1H); MS (DCI/NH_3) m/z 176 $(M+H)^+$; Anal. calculated for $C_{16}H_{20}N_4O_3S$•0.25 TsOH•0.85 H_2O: C, 52.41; H, 5.87; N, 13.77. Found C, 52.45; H, 5.88; N, 13.69.

Example 27

(1R,4R)-2-(6-chloro-3-pyridinyl)-5-cyanomethyl-2,5-diazabicyclo[2.2.1]heptane

4-methylbenzenesulfonate

The product from Example 15D (140 mg, 0.37 mmole) in DMF (5 mL) was treated with triethylamine (0.26 mL, 1.8 mmole) and bromoacetonitrile (0.03 mL, 0.43 mmole) under a nitrogen atmosphere. After stirring for 72 hours at ambient temperature, the reaction mixture was poured into saturated. aqueous Na_2CO_3 (30 mL) and extracted with ether (5x50 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on SiO_2 ($CHCl_3$ /MeOH/ NH_4OH 95:4.5:0.5)

and combined with 4-methylbenzenesulfonic acid (21 mg, 0.11 mmole) to provide the title compound (47 mg, 30% yield). ^{1}H NMR (D_2O, 300 MHz) δ 2.14 (m, 2H), 2.39 (s, 3H), 3.34-3.48 (m, 2H), 3.36 (d, J=9.03 Hz 1H), 3.62 (m, 1H), 3.93-3.95 (m. 2H), 4.10 (br s, 1H), 4.52 (br s, 1H), 7.17 (dd, J=2.84,7.72 Hz, 1H) 7.28-7.38 (m, 3H), 7.69 (d, J=8.11 Hz, 2H)7.77 (d, J=2.94 Hz, 1H); MS (DCI/NH_3) m/z 249 $(M+H)^+$, 266 $(M+NH_4)^+$; Anal calculated for $C_{12}H_{13}N_4Cl \bullet C_7H_8O_3S \bullet 0.1\ H_2O$: C, 53.99; H, 5.05; N, 13.25. Found C, 53.99; H, 5.19; N, 13.19.

Example 28

(1S,4S)-2-(6-nitro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane

The product from Example 3A was treated with trifluoroacetic acid:methylene chloride (1:2) at ambient temperature for 2 hours. The volatiles were removed under reduced pressure, and the residue was purified on SiO_2 (5%MeOH/CH_2Cl_2/1%NH_4OH) to provide the title compound as a yellow gum. MS (DCI/NH_3) m/z 221 $(M+H)^+$, 238 $(M+NH_4)^+$.

Example 29

(1S,4S)-2-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 29A

tert-butyl (1S,4S)-5-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 2A (0.885 g, 2.85 mmol) in MeOH (14 mL) and triethylamine(0.55 mL) was treated with 10%Pd/C (0.02 g) and stirred under a hydrogen atmosphere (60 psi) at 50 °C for 80 minutes. The catayst was removed by filtration and the filtrate was concentrated. The residue was purified on SiO_2 (5%MeOH/CH_2Cl_2) to provide the title compound (0.72 g, 92%) as a white solid. MS (DCI/NH_3) m/z 276 $(M+H)^+$.

Example 29B

(1S,4S)-2-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 29A was processed as described in Example 2B to provide the title compound. ^{1}H NMR (MeOH, 300 MHz) δ 2.13(d, J=13.0 Hz, 1H), 2.28-2.40 (m, 3H), 3.68-3.87 (m, 2H), 4.62 (s, 1H), 5.11 (s, 1H), 7.36 (dd, J=1.0,9.0 Hz, 1H), 7.60-7.68 (m, 1H), 8.60 (dd, J=1.0,5.0 Hz, 1H); MS (DCI/NH_3) m/z 176 $(M+H)^+$; Anal. calculated for $C_{16}H_{20}N_4O_3S$•0.25 TsOH•0.85 H_2O: C, 52.34; H, 5.85; N, 13.49. Found C, 52.29; H, 6.03; N, 13.52.

Example 30

(1S,4S)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 30A

tert-butyl (1S,4S)-5-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.300 g, 1.01 mmol), prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), in anhydrous toluene (30ml) was treated with 2-fluoro-5-iodopyridine (0.34g, 1.52 mmol), available as described in (US 5,733,912), $Pd_2(dba)_3$ (0.028 g, 0.03 mmol), (S)-(-)-2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl (0.028 g, 0.06 mmol), available from Strem Chemicals, and sodium tert-butoxide (0.248 g, 2.58 mmol). The reaction mixture was heated at 80°C for 5 hours. The reaction mixture was poured into diethyl ether (100 mL), washed with brine (100ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (3%MeOH/CH_2Cl_2) to provide the title compound (0.095g, 21% yield) as a yellow oil. MS (DCI/NH_3) m/z 276 $(M+H)^+$.

Example 30B

(1S,4S)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product from Example 30A was processed as described in Example 2B to provide the title compound. ^{1}H NMR(MeOD, 300 MHz) δ 2.06 (d, J=12.0 Hz, 1H), 2.29 (d, J=12.0 Hz, 1H), 3.25-3.30 (m, 1H). 3.35 (s, 2H), 3.73 (dd, J=3.0, 12.0 Hz, 1H), 4.50 (s, 1H), 4.68(3, 1H), 6.96 (dd, J=3.0, 9.0 Hz, 1H), 7.28-7.38 (m, 1H), 7.52-7.54 (m, 1H); MS (DCI/NH_3) m/z 194 $(M+H)^+$; Anal. calculated for $C_{24}H_{28}N_3O_6S_2F$•0.75 TsOH•1.15 H_2O: C, 51.10; H, 5.32; N, 6.11. Found C, 51.11; H, 5.54; N, 6.10.

Example 31

(1S,4S)-2-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 31A

tert-butyl (1S,4S)-5-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), and 3,5-dibromopyridine (purchased from Avocado Research Chemicals, Ltd.) were coupled according to the procedure described in Example 1A to provide the title compound. MS (DCI/NH_3) m/z 354 $(M+H)^+$.

Example 31B

(1S,4S)-2-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product of Example 31A was processed as described in Example 2B to provide the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92-2.10 (m, 2H), 3.21 (s, 2H), 3.60-3.71 (m, 2H), 4.05 (s, 1H), 4.38 (s, 1H), 6.97 (t, J=1.0 Hz, 1H), 7.90 (d, J=2.0 Hz, 1H), 8.03 (d, J=1.0 Hz, 1H); MS (DCI/NH_3) m/z 254 $(M+H)^+$; Anal. calculated for $C_{17}H_{20}N_3O_3SBr$•0.30 TsOH: C, 47.99; H, 4.72; N, 8.79. Found C, 48.02; H, 4.95; N, 8.87.

Example 32

(1S,4S)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane

4-methylbenzenesulfonate

Example 32A

tert-butyl (1S,4S)-5-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product of Example 31A (2.89g, 8.2 mmol) in anhydrous/degassed DMF (60ml) was treated with $Zn(CN)_2$ (0.481g, 4.1 mmol), and tetrakis(triphenylphosphine)-palladium(0) (0.95g, 0.8 mmol). The mixture was heated at 80°C for 16 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to ambient temperature and poured into diethyl ether (150ml). The organics were washed with brine/H_2O (1/1) (200ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on SiO_2 (5% MeOH/CH_2Cl_2) to provide the title compound (1.90 g, 77% yield) as a white solid. MS (DCI/NH_3) m/z 301 $(M+H)^+$.

Example 32B

(1S,4S)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane

4-methylbenzenesulfonate

The product from Example 32A was processed as described in Example 2B to provide the title compound. ^1H NMR (MeOD, 300 MHz) δ 2.0 (d, J=13.0 Hz, 1H), 2.21 (d, J=13.0 Hz, 1H), 3.38 (s, 2H), 3.42 (d, J=1.0 Hz, 1H), 3.75 (dd, J=3.0, 12.0 Hz, 1H), 4.56 (s, 1H), 4.82 (s, 1H), 7.48 (t, J=1.0 Hz, 1H), 8.19-8.31 (m, 2H); MS (DCI/NH_3) m/z 201 $(M+H)^+$; Anal. calculated for $C_{18}H_{20}N_4O_3S$: C, 58.05; H, 5.41; N, 15.04. Found C, 57.84; H, 5.47; N, 14.81.

Example 33

(1R,4R)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane

4-methylbenzenesulfonate

Example 33A

tert-butyl (1R,4R)-5-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 2-fluoro-5-iodopyridine were processed as described in Example 30A to provide the title compound. MS (DCI/NH_3) m/z 294 $(M+H)^+$.

Example 33B

(1R,4R)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product of Example 33A was processed as described in Example 2B to provide the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.75 (d, J=12.0 Hz, 1H), 1.96 (d,J=12.0 Hz, 1H), 2.92 (d, J=9.0 Hz, 1H), 3.07 (s, 2H), 3.66 (dd, J=3.0, 9.0 Hz, 1H), 3.81 (s, 1H), 4.26 (s, 1H), 6.78 (dd, J=1.0, 6.0 Hz, 1H), 6.92-7.0 (m, 1H), 7.45 (t, J=1.0 Hz, 1H); MS (DCI/NH_3) m/z 194 $(M+H)^+$, 211 $(M+NH_4)^+$; Anal. calculated for $C_{17}H_{20}N_3O_3SF$: C, 55.20; H, 5.59; N, 11.36. Found C, 55.21; H, 5.61; N, 11.13.

Example 34

(1S,4S)-2-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane trihydrochloride

Example 34A

tert-butyl (1S,4S)-5-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 32A (0.267g, 0.89 mmol) in 30% NH_3/methanol was treated with Raney-Nickel (0.10g). The reaction mixture was stirred at ambient temperature under a hydrogen atmosphere (60 psi) for 4 hours. The mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2; 10% MeOH/CH_2Cl_2/1% NH_4OH) to provide the title compound (0.199 g, 73% yield) as a white solid. MS (DCI/NH_3) m/z 305 $(M+H)^+$.

Example 34B

(1S,4S)-2-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane trihydrochloride

The product from Example 34A (0.199 g, 0.65 mmol) in EtOH (5 mL) was treated with 4N HCl/dioxane (5 mL). After stirring at ambient temperature for 1 hour, the volatiles were removed under reduced pressure to provide the title compound (0.042 g, 20% yield) as a white solid. ^{1}H NMR($CDCl_3$, 300 MHz) δ 2.18 (d, J=12.0 Hz, 1H), 2.34 (d, J=12.0 Hz, 1H), 3.45-3.58 (m, 3H), 3.83 (d, J=15.0 Hz, 1H), 4.32 (s, 2H), 4.68 (s, 1H), 4.89 (s, 1H), 7.68 (s, 1H), 8.11 (s, 1H), 8.15 (s, 1H); MS (DCI/NH_3) m/z 205 $(M+H)^+$; Anal. calculated for $C_{11}H_{16}N_4 \cdot 3.6$ HCl•0.45 EtOH: C, 40.12; H, 6.31; N, 15.73. Found C, 40.22; H, 6.20; N, 15.72.

Example 35

2-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane trihydrochloride

Example 35A

benzyl 3-oxo-2,6-diazabicyclo[3.2.1]octane-6-carboxylate

Benzyl 5-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (2.46 g, 10.0 mmol), prepared according to the procedures described by (Carroll, F. I.; et. al., J. Med. Chem. (1992) 35, 2184), in 50 mL of 95% aqueous ethanol at ambient temperature was treated with sodium acetate (2.47 g, 30.1 mmol) and hydroxylamine hydrochloride (3.48 g, 50.1 mmol). After 45 minutes, the mixture was concentrated under reduced pressure and the residue was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic extract was dried ($MgSO_4$) and concentrated to afford 2.50 grams (96%) of a mixture of the desired oximes as a white solid. A portion of this material (1.57 g, 6.03 mmol) was stirred in a 5:1 solution of CH_2Cl_2/trimethylsilylpolyphosphate for 12 hours at ambient temperature. The solution was diluted with H_2O and extracted twice with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; 95:5 CH_2Cl_2/MeOH) to provide 1.08 grams (68%) of the title compound as a white solid. MS (DCI/NH_3) m/z 261 $(M+H)^+$, 278 $(M+NH_4)^+$.

Example 35B

benzyl 2,6-diazabicyclo[3.2.1]octane-6-carboxylate

The product from example 35A (800 mg, 3.07 mmol) in THF (12 mL) at 0 °C was treated dropwise with a 2.0 M solution of borane-methyl sulfide complex in THF (3.4 mL, 6.8 mmol). The solution was stirred for 14 hours at ambient temperature, then recooled to 0 °C and quenched by the careful addition of MeOH and concentrated under reduced pressure. The residue was dissolved in toluene (12 mL) and treated with n-propylamine (1.7 mL). The mixture was stirred for 3 hours at 60 °C, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (4X). The organic extracts were combined, dried (K_2CO_3), and concentrated. The residue was purified by chromatography (silica gel; 90:10:1 CH_2Cl_2/MeOH/NH_4OH) to provide 453 mg (60%) of the title compound as a colorless oil. MS (DCI/NH_3) m/z 247 $(M+H)^+$.

Example 35C

benzyl 2-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane-6-carboxylate

The product from Example 35B and 2-chloro-5-iodopyridine were processed as described in Example 1A to provide the title compound (30% yield) as a light yellow oil. MS (DCI/NH_3) m/z 358, 360 $(M+H)^+$.

Example 35D

2-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane trihydrochloride

The product from Example 35C (62 mg, 0.17 mmol) in acetonitrile (3 mL) at 0 °C was treated with iodotrimethylsilane (37 mL, 0.26 mmol). The solution was stirred at 0 °C for 3 hours, quenched with MeOH, and concentrated under reduced pressure. The residue was diluted with 1N aqueous HCl and extracted with EtOAc (2X). The aqueous phase was basified with 10% aqueous NaOH and extracted with 3:1 CH_2Cl_2/iPrOH (4X). The extracts were combined, dried (K_2CO_3), and concentrated to provide a light yellow oil. The oil was diluted with EtOH and treated with a solution of HCl in diethyl ether. The resulting precipitate was collected, triturated with diethyl ether, and dried under high vacuum to provide the title compound as a light yellow solid. ^1H NMR (DMSO-d_6, 300

Hz) δ 1.80-2.02 (m, 4H), 3.00 (m, 1H), 3.34-3.40 (m, 2H), 3.60 (m, 1H), 4.15 (m, 1H), 4.68 (m, 1H), 7.33 (d, J=8.8 Hz, 1H), 7.43 (dd, J=3.3, 8.8 Hz, 1H), 8.08 (d, J=3.0 Hz, 1H); MS (CI/NH_3) m/z 224, 226 $(M+H)^+$; Anal. Calcd for $C_{11}H_{14}ClN_3 \cdot 3\ HCl \cdot 1.2\ H_2O$: C, 37.25; H, 5.51; N, 11.85. Found: C, 36.99; H, 5.21; N, 12.13.

Example 36

3-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane hydrochloride

The product from Example 37A (1.15 g, 4.6 mmol) in chloroform (10 mL) was treated with α-chloroethyl chloroformate (1.1 eq.) at 0 °C. The solution was allowed to warm to ambient temperature over 0.5 hours and then heated at reflux for one hour. The mixture was allowed to cool to ambient temperature and concentrated under reduced pressure. The residue was dissolved in methanol (20 mL) and heated at reflux for one hour. The solvent was removed under reduced pressure to provide a solid that was recrystallized from ethanol to provide the title compound (1.03 g, 83% yield). ^{1}H NMR (CD_3OD, 300 MHz) δ 1.72-1.84 (m, 1H), 1.87-2.0 (m, 1H), 2.0-2.36 (m, 4H), 3.5-3.65 (m, 2H), 3.65-3.78 (m, 1H), 3.8-3.9 (br d, J=15 Hz, 1H), 4.22 (br s, 2H), 7.25 (d, J=12 Hz, 1H), 7.38 (dd, J=4.5, 12 Hz, 1H), 7.97 (d, J=4.5 Hz, 1H); MS (DCI/NH_3) m/z 238 $(M+H)^+$, 255 $(M+NH_4)^+$; Anal. Calcd for $C_{12}H_{16}ClN_3 \cdot HCl$: C, 52.57; H, 6.25; N, 15.32. Found: C, 52.82; H, 6.33; N, 15.32.

Example 37

9-methyl-3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane 4-methylbenzenesulfonate

Example 37A

9-methyl-3-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane

9-Methyl-3,9-diazabicyclo[4.2.1]nonane (prepared as described in U.S. Patent 2,999,091) and 2-chloro-5-iodopyridine were coupled according the procedure of Example 15C to provide the title compound (78% yield). ^{1}H NMR (free base, $CDCl_3$, 300 MHz) δ 1.23-1.48 (m, 2H), 1.65-1.76 (m, 1H), 1.91-2.27 (m, 3H), 2.44 (s, 3H), 3.18-

3.35 (m, 3H), 3.48-3.54 (m, 2H), 3.65 (br d, J=13.5 Hz, 1H), 6.98 (dd, J=3, 8.25 Hz, 1H), 7.06 (d, J=8.25 Hz, 1H), 7.87 (d, J=3 Hz, 1H); MS (DCI/NH_3) m/z 252 $(M+H)^+$, 269 $(M+NH_4)^+$; Anal. Calcd for $C_{13}H_{18}ClN_3 \cdot C_7H_8O_3S$: C, 56.66; H, 6.18; N, 9.91. Found: C, 56.76; H, 6.15; N, 9.77.

Example 37B

9-methyl-3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane 4-methylbenzenesulfonate

The product from Example 37A (641 mg), was treated with 10% Pd/C (61.8 mg) in methanol (11 mL) and triethyl amine (0.64 mL) under a hydrogen atmosphere (60 psi) at 50 °C for one hour. The mixture was filtered and concentrated under reduced pressure to provide a solid. The resulting solid was taken up in EtOAc and washed with saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to provide the free base (91 % yield). The free base was treated with 4-methylbenzenesulfonate (1.0 eq) and the obtained solid was recrystallized from ethanol/ethyl acetate. ^1H NMR (CD_3OD, 300 MHz) δ 1.83-1.93 (m, 1H), 1.93-2.11 (m, 2H), 2.15-2.29 (m, 1H), 2.37 (s, 3H), 2.44-2.56 (m, 2H), 2.95 (s, 3H), 3.61-3.82 (m, 4H), 4.02-4.15 (m, 2H), 7.23 (d, J=7.5 Hz, 2H), 7.29 (dd, J=4.5, 7.5 Hz, 1H), 7.69 (d, J=7.5 Hz, 2H), 7.94 (dd, J=1.5, 4.5 Hz, 1H), 8.2 (d, J=3 Hz, 1H); MS (DCI/NH_3) m/z 218 $(M+H)^+$, 235 $(M+NH_4)^+$; Anal. Calcd for $C_{13}H_{19}N_3 \cdot C_7H_8O_3S$: C, 61.67; H, 6.99; N, 10.79. Found: C, 61.50; H, 7.03; N, 10.76.

Example 38

(1S,4S)-2-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 38A

tert-butyl (1S,4S)-5-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product of Example 32A (0.43 g, 1.43 mmol) in ethanol (20 mL) was treated with 30% H_2O_2 (1.40 mL) and 6N NaOH (1.40 mL) and heated at 50 °C for 2 hours. The

mixture was poured into 15% NaOH (50 mL) and extracted with CH_2Cl_2 (150 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on SiO_2 (5% MeOH/CH_2Cl_2) to provide the title compound (0.20 g, 44%) as a white solid. MS (DCI/NH_3) m/z 319 $(M+H)^+$.

Example 38B

(1S,4S)-2-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product of Example 38A was processed as described in Example 2B to provide the title compound. ^1H NMR (MeOD, 300 MHz) δ 2.12 (d, J=15.0 Hz, 1H), 2.32 (d, J=15.0 Hz, 1H), 3.42 (s, 2H), 3.79 (dd, J=2.0, 10.0 Hz, 1H), 4.60 (s, 1H), 4.88 (s, 1H), 7.70 (t, J=1.0 Hz, 1H), 8.21 (d, J=3.0 Hz, 1H), 8.42 (d, J=1.0 Hz, 1H); MS (DCI/NH_3) m/z 219 $(M+H)^+$; Anal. calculated for $C_{24}H_{30}N_4O_6S_2$: C, 52.27; H, 5.73; N, 11.55. Found C, 51.92; H, 5.66; N, 10.48.

Example 39

(1R,4R)-2-(5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 39A

tert-butyl (1R,4R)-5-(5-benzyloxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 5-(benzyloxy)-3-bromo-pyridine, prepared as described in (US 5,733,912) were coupled according to the procedure described in Example 15C to provide the title compound. MS (DCI/NH_3) m/z 382 $(M+H)^+$.

Example 39B

(1R,4R)-2-(5-benzyloxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane

The product from Example 39A (0.52 g, 1.36 mmol) in EtOH (10 mL) was treated with 4N HCl/dioxane (10 mL) and stirred at ambient temperature for 1 hour. The volatiles were removed under reduced pressure and the residue was purified on SiO_2

(10% MeOH/CH_2Cl_2/1% NH_4OH) to provide the title compound (0.347 g, 90% yield) as a white solid. MS (DCI/NH_3) m/z 282 $(M+H)^+$.

Example 39C

(1R,4R)-2-(5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane

The product from Example 39B (0.347 g, 1.23 mmol) in EtOH (10 mL) was treated with 10% Pd/C (10 mg) and stirred at ambient temperature under a hydrogen atmosphere (1 atm) for 16 hours. The catalyst was filtered, washed with EtOH (10 mL) and the combined filtrate was concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2/1% NH_4OH) to provide the free base of the title compound (0.168 g, 71% yield) as a light yellow solid. The free base was dissolved in EtOH and treated with a solution of para-toluenesulfonic acid (0.167g, 1 eq) in a minimum volume of EtOH. The solution was concentrated under reduced pressure to provide the title compound (330 mg, 71% yield) as an off-white foam. ^1H NMR (MeOD, 300 MHz) δ 2.05(d, J=13.0 Hz, 1H), 2.28 (d, J=13.0 Hz, 1H), 3.32-3.36 (m, 3H), 3.70 (dd, J=3.0,10.0 Hz, 1H), 4.51 (s, 1H), 4.67 (s, 1H), 6.55 (t, J=2.0 Hz, 1H), 7.51 (d, J=2.0 Hz, 1H), 7.53 (d, J=2.0 Hz, 1H); MS (DCI/NH_3) m/z 192 $(M+H)^+$; Anal. calculated for $C_{17}H_{21}N_3O_4S \cdot 0.8\ H_2O$: C, 54.04; H, 6.03; N, 11.12. Found C, 54.15; H, 6.11; N, 10.83.

Example 40

(1R,4R)-2-(6-chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 40A

5-bromo-3-pyridinol

3-(Benzyloxy)-5-bromopyridine (15.0g, 56.8 mmol), prepared as described in (US 5,733,912), and 30% HBr/HOAc (200 mL) were stirred at ambient temperature for 16 hours. The reaction mixture was diluted with diethyl ether (500 mL) and the resulting white solid (12.9 g) was isolated by filtration. The solid, in methanol (300 ml), was treated with concentrated NH_4OH (50 mL). After stirring at ambient temperature for 12

hours, the reaction mixture was concentrated under reduced pressure to provide the title compound (9.8 g, 89%) as a white solid. MS (DCI/NH_3) m/z 174, 176 $(M+H)^+$.

Example 40B

5-bromo-2-chloro-3-pyridinol

The product from Example 40A (9.8g, 56.3 mmol) and NaOH (2.40 g, 100 mmol) in water (100mL) were treated with NaOCl (35 ml of 10% solution). The reaction mixture was stirred at ambient temperature for 16 hours and then quenched with acetic acid (5 ml), extracted with ethyl acetate (500mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on SiO_2 (3% MeOH/CH_2Cl_2) to provide the title compound (11.20 g, 96% yield) as a yellow solid. MS (DCI/NH_3) m/z 208, 210 $(M+H)^+$.

Example 40C

5-bromo-2-chloro-3-(methoxymethoxy)pyridine

The product from Example 40B (11.2 g, 53.1 mmol) in diethyl ether (50 mL) was added to a suspension of NaH (1.69 g, 70 mmol) in DMF (300 mL) and diethyl ether (60 mL). The mixture was stirred at ambient temperature for 30 minutes and then treated with a solution of chloromethyl methyl ether (5.65 g, 70 mmol, Aldrich Chemical Co.) in diethyl ether (30 mL). After stirring at ambient temperature for 2 hours, the mixture was quenched by cautious addition of water (200 mL). The aqueous mixture was extracted with diethyl ether (300 mL), and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on SiO_2 (ethyl acetate/hexane (1/4)) to provide the title compound (8.29 g, 61% yield) as a colorless oil. MS (DCI/NH_3) m/z 252, 254 $(M+H)^+$.

Example 40D

tert-butyl (1R,4R)-5-(6-chloro-5-methoxymethoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B (1.0 g, 5.0 mmol) in anhydrous toluene (50 mL) was treated with the product from Example 40C (1.27g, 5.0 mmol), $Pd_2(dba)_3$ (0.093 g, 0.1 mmol), BINAP (0.126 g, 0.2 mmol) and sodium tert-butoxide (0.83 g, 8.6 mmol). The reaction mixture was heated at 80 °C for 4 hours. The mixture was allowed to cool to ambient temperature, diluted with ether (100 mL), washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (5% MeOH/CH_2Cl_2) to provide the title compound (1.0 g, 52% yield) as a yellow oil. MS (DCI/NH_3) m/z 370 $(M+H)^+$.

Example 40E

(1R,4R)-2-(6-chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

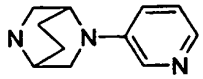
The product from Example 40D (0.60 g, 1.62 mmol) in acetonitrile (8 mL) was treated with Amberlist resin (7.5 g) and shaken at ambient temperature for 48 hours. The resin was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified on SiO_2 (10% MeOH/CH_2Cl_2/1% NH_4OH) to provide the free base of the title compound (0.121 g) as a white solid. The free base in EtOH was treated with 4-methylbenzenesulfonic acid (0.102 g, 1 eq.) for 10 minutes. The solvent was removed under reduced pressure to provide the title compound (222 mg, 33% yield) as a white solid: ^{1}H NMR (MeOD, 300 MHz) δ 2.06 (d, J=12.0 Hz, 1H), 2.37 (d, J=12.0 Hz, 1H), 3.28-3.35 (m, 3H), 3.70 (dd, J=3.0,12.0 Hz, 1H), 4.51 (s, 1H), 4.65 (s, 1H), 6.65 (d, J=3.0 Hz, 1H), 7.35 (d, J=3.0 Hz, 1H); MS (DCI/NH_3) m/z 226 $(M+H)^+$, 243 $(M+NH_4)^+$; Anal. Calculated for $C_{17}H_{20}N_3O_4SCl$•0.2 TsOH•0.60 H_2O: C, 49.87; H, 5.19; N, 9.48. Found C, 49.86; H, 5.36; N, 9.52.

Example 41

3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane bis(4-methylbenzenesulfonate)

The product from Example 36 (1.6 mmol) was hydrogenated according to the procedure of Example 37B to provide the free base (86% yield). This was combined with 4-methylbenzenesulfonate (2.0 eq) and the obtained solid was recrystallized from

ethanol/ethyl acetate to provide the title compound. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.73-1.83 (m, 1H), 1.92-2.35 (m, 5H), 2.47 (s, 3H), 3.71-3.82 (m, 3H), 3.94 (br d, J=15 Hz, 1H), 4.27 (br d, J=15 Hz, 2H), 7.23 (d, J=7.5 Hz, 4H), 7.69 (d, J=7.5 Hz, 4H), 7.80 (m, 1H), 8.0-8.09 (m, 2H), 8.48 (d, J=3 Hz, 1H); MS (DCI/NH_3) m/z 204 $(M+H)^+$, 221 $(M+NH_4)^+$; Anal. Calcd for $C_{12}H_{17}N_3 \cdot C_{14}H_{16}O_6S_2$: C, 57.02; H, 6.07; N, 7.67. Found: C, 56.88; H, 6.17; N, 7.57.



Example 42

2-(3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane dihydrochloride

Example 42A

tert-butyl 5-(3-pyridinyl)-2,5-diazabicylo[2.2.2]octane-2-carboxylate

2-5-Diazabicyclo[2.2.2]octane (390 mg, 3.5 mmole), prepared by the method of Sturm and Henry (J. Med. Chem. (1974), 17, 481), was treated with 3-bromopyridine (545 mg, 3.5 mmole), BINAP (92 mg, 0.14 mmole), $Pd_2(dba)_3$ (40 mg, 0.07 mmole) and sodium tert-butoxide (431 mg 4.5 mmole) in toluene (10 mL) under a nitrogen atmosphere. After heating the mixture at 75 °C 5 °C for 2 hours, the mixture was allowed to cool to ambient temperature and treated with di-tert-butyl-dicarbonate (1.5 g, 6.9 mmole) and then allowed to stir an additional 16 hours. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2, hexanes:ethyl acetate 9:1 to1:1) to provide the title compound (193 mg, 19% yield). MS (DCI/NH_3) m/z 290 $(M+H)^+$, 307 $(M+NH_4)^+$.

Example 42B

2-(3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane dihydrochloride

The product from Example 42A (137 mg, 0.6 mmole) was treated with a 1:1 mixture of CH_2Cl_2 and TFA (3 mL). After two hours, the solvent was removed under reduced pressure and the residue purified by chromatography (SiO_2, $CHCl_3$:MeOH:NH_4OH 95:5:0 to 95:4.5:0.5) to provide the free base. The free base was

treated with excess 1M HCl in diethyl ether to provide the title compound (65 mg, 37% yield). ^{1}H NMR (CD_3OD, 300 MHz) δ 2.04-2.17 (m, 2H), 2.21-2.25 (m, 2H), 3.5-3.69 (m, 3H), 3.90 (d, J=11.63 Hz 1H), 4.00 (br s, 1H), 4.45 (br s, 1H), 7.87 (dd, J=5.01,8.82Hz, 1H), 7.94 (dd, J=1.01, 9.16 Hz, 1H), 8.00 (d, J=5.08 Hz, 1H), 8.28 (d, J=1.70 Hz, 1H); MS (DCI/NH_3) m/z 190 $(M+H)^+$, 207 $(M+NH_4)^+$; Anal. Calculated for$C_{11}H_{15}N_3 \bullet 2.1$ HCl$\bullet 0.4$ $C_4H_8O_2$: C, 50.27; H, 6.80; N, 13.96. Found: C, 50.05; H, 7.12; N, 14.34.

Example 43

(1S,4S)-2-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 43A

3-bromo-5-methoxypyridine

A suspension of NaH (0.47 g, 19.6 mmol) in DMF (20 mL) was cautiously treated with methanol (0.59 g, 18.4 mmol). After 30 minutes, the mixture was treated with a solution of 3,5-dibromopyridine (4.0 g, 16.9 mmol) in DMF (5.0 mL). After stirring overnight, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether (200 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (CH_2Cl_2) to provide the title compound (2.24 g, 70% yield) as a yellow solid.

Example 43B

tert-butyl (1S,4S)-5-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), and the product from Example 43A were coupled according to the procedure described in Example 1A to provide the title compound. MS (DCI/NH_3) m/z 306 $(M+H)^+$.

Example 43C

(1S,4S)-2-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product from Example 43B was processed as described in Example 2B to provide the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82-2.01 (m, 2H), 3.02 (d, J=10 Hz, 1H), 3.08 (s, 2H), 3.63 (dd, J=3.0,9.0 Hz, 1H), 3.82 (s, 3H), 3.87 (s, 1H), 4.32 (s, 1H), 6.33 (t, J=2.0 Hz, 1H), 7.64 (d, J=3.0 Hz, 1H), 7.68 (d, J=2.0 Hz, 1H); MS (DCI/NH_3) m/z 206 $(M+H)^+$; Anal. calculated for $C_{25}H_{31}N_3O_7S_2 \cdot 0.78\ H_2O$: C, 52.89; H, 5.86; N, 7.40. Found C, 52.63; H, 5.91; N, 7.12.

Example 44

(1R,4R)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 44A

tert-butyl (1R,4R)-5-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 3,5-dibromopyridine were processed as described in Example 1A to provide the title compound.

Example 44B

tert-butyl (1R,4R)-5-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 44A was processed as described in Example 32A to provide the title compound. MS (DCI/NH_3) m/z 301 $(M+H)^+$.

Example 44C

(1R,4R)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product of Example 44B was processed as described in Example 2B to provide the title compound. ^{1}H NMR (MeOD, 300 MHz) δ 2.10 (dt, J=1.0, 11.0 Hz, 1H), 2.31 (dt, J=1.0, 11.0 Hz, 1H), 3.38 (d, J=2.0 Hz, 2H), 3.42 (d, J=1.0 Hz, 1H), 3.75 (dd, J=3.0, 9.0 Hz, 1H),4.56 (s, 1H), 4.82(s, 1H), 7.50 (dd, J=1.0, 4.0 Hz, 1H), 8.23 (d,

J=4.0 Hz, 1H), 8.25 (d, J=3.0 Hz, 1H); MS (DCI/NH_3) m/z 201 $(M+H)^+$, 218 $(M+NH_4)^+$; Anal. calculated for $C_{18}H_{20}N_4O_3S \cdot 0.50\ H_2O$: C, 56.68; H, 5.55; N, 14.69. Found C, 56.92; H, 5.48; N, 14.29.

Example 45

(1S,4S)-2-(6-chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 45A

tert-butyl (1S,4S)-5-(6-chloro-5-methoxymethoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem. (1988) 31, 1598-1611), and the product from Example 40C were processed as described in Example 40D to provide the title compound. MS (DCI/NH_3) m/z 370 $(M+H)^+$.

Example 45B

(1S,4S)-2-(6-chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 45A (1.00 g, 2.7 mmol) in EtOH (2.0 mL) was treated with 4N HCl/dioxane (5 mL) and then heated at 60 °C for 4 hours. The reaction mixture was allowed to cool to ambient temperature and then concentrated under reduced pressure. The residue was purified on SiO_2 (10% MeOH/CH_2Cl_2/1% NH_4OH) to provide the free base of the title compound (0.424 g) as a light yellow solid. The free base was treated with 4-methylbenzenesulfonic acid (0.356 g, 1 eq) in a minimum amount of EtOH for 10 minutes then concentrated under reduced pressure to produce the title compound (0.78 g, 72% yield) as a white solid. ^1H NMR (MeOD, 300 MHz) δ 2.08 (d, J=12.0 Hz, 1H), 2.28 (d, J=12.0 Hz, 1H), 3.32-3.38 (m, 3H), 3.70 (dd, J=3.0,12.0 Hz, 1H), 4.52 (t, J=1.0 Hz, 1H), 4.65 (s, 1H), 6.64 (d, J=3.0 Hz, 1H), 7.32 (d, J=3.0 Hz, 1H); MS (DCI/NH_3) m/z 226 $(M+H)^+$, 243 $(M+NH_4)^+$; Anal. calculated for $C_{17}H_{20}N_3ClO_4S \cdot 3.0\ H_2O$: C, 45.18; H, 5.80; N, 9.30. Found C, 45.12; H, 5.68; N, 9.29.

Example 46

(1R,4R)-2-(6-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 46A

tert-butyl (1R,4R)-5-(6-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 2-methoxy-5-bromopyridine (purchased from Frontier Scientific) were processed as described in Example 15C to provide the title compound. MS (DCI/NH_3) m/z 306 $(M+H)^+$.

Example 46B

(1R,4R)-2-(6-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 46A was processed as described in Example 2B to provide the title compound. ^1H NMR (MeOD, 300 MHz) δ 2.05 (d, J=11.0 Hz, 1H), 2.28 (d, J=11.0 Hz, 1H), 3.25 (dd, J=3.0, 12.0 Hz, 1H), 3.35 (s, 2H), 3.72 (dd, J=3.0, 12.0 Hz, 1H), 3.78(s, 3H), 4.48 (t, J=1.0 Hz, 1H), 4.61 (s, 1H), 6.84 (d, J=11.0 Hz, 1H), 7.28 (dd, J=3.0, 9.0 Hz, 1H), 7.53 (d, J=3.0 Hz, 1H); MS (DCI/NH_3) m/z 206 $(M+H)^+$; Anal. calculated for $C_{18}H_{23}N_3O_4S \cdot 0.45.0\ H_2O$: C, 56.07; H, 6.25; N,10.90. Found C, 56.14; H, 6.12; N, 10.52.

Example 47

(1R,4R)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 47A

tert-butyl (1R,4R)-5-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 2-chloro-5-iodo-3-methylpyridine, prepared as described in (US 5,733,912) were processed as described in Example 15C to provide the title compound. MS (DCI/NH_3) m/z 324 $(M+H)^+$.

Example 47B

(1R,4R)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 47A was processed as described in Example 2B to provide the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.89 (d, J=10.0 Hz, 1H), 1.98 (d, J=10.0 Hz, 1H), 2.31 (s, 3H), 3.00 (dd, J=1.0, 10.0 Hz, 1H), 3.09 (s, 2H), 3.63 (dd, J=3.0, 9.0 Hz, 1H), 3.88 (s, 1H), 4.29 (s, 1H), 6.72 (d, J=2.0 Hz, 1H), 7.56 (d, J=3.0 Hz, 1H); MS (DCI/NH_3) m/z 224 $(M+H)^+$; Anal. calculated for $C_{18}H_{22}N_3O_3SCl \cdot 0.2\ H_2O$: C, 54.12; H, 5.65; N, 10.52. Found C, 54.21; H, 5.80; N, 10.18.

Example 48

(1R,4R)-2-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 48A

tert-butyl (1R,4R)-5-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 2,3-dichloro-5-iodopyridine, prepared as described in (US 5,733,912) were processed as described in Example 15C to provide the title compound. MS (DCI/NH_3) m/z 344 $(M+H)^+$.

Example 48B

(1R,4R)-2-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 48A was processed as described in Example 2B to provide the title compound. ^1H NMR (MeOD, 300 MHz) δ 2.07 (m, 1H), 2.30 (m, 1H), 3.28-3.34 (m, 1H), 3.47 (s, 2H), 3.72 (dd, J=2.0, 10.0 Hz, 1H), 4.53 (t, J=1.0 Hz, 1H),

4.75 (s, 1H), 7.36 (d, J=3.0 Hz, 1H), 7.77 (d, J=3.0 Hz, 1H); MS (DCI/NH_3) m/z 244 $(M+H)^+$; Anal. calculated for $C_{17}H_{19}N_3O_3SCl_2 \cdot 0.05$ EtOH: C, 49.06; H, 4.65; N, 10.04. Found C, 49.22; H, 5.04; N, 11.05.

Example 49

6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane bis(4-methylbenzenesulfonate)

Example 49A

tert-butyl 2,6-diazabicyclo[3.2.1]octane-2-carboxylate

The product from Example 35B (140 mg, 0.568 mmol) in CH_2Cl_2 at ambient temperature was treated with triethylamine followed by di-tert-butyl dicarbonate. The solution was stirred for 2 hours, diluted with saturated aqueous K_2CO_3, and extraced with CH_2Cl_2 (2X). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide 190 mg a colorless oil. A suspension of the oil and 10% Pd/C (20 mg) in MeOH (10 mL) were stirred under one atmosphere of hydrogen (balloon) for 6 hours. The catalyst was removed by filtration through a plug of Celite (CH_2Cl_2 wash). The filtrate was concentrated to provide (106 mg, 91%) the title compound as a colorless oil. MS (DCI/NH_3) m/z 213 $(M+H)^+$, 230 $M+NH_4)^+$.

Example 49B

tert-butyl 6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane-2-carboxylate

The product from Example 49A and 2-chloro-5-iodopyridine were processed as described in Example 1A to provide the title compound (30% yield) as a light yellow oil. MS (DCI/NH_3) m/z 324, 326 $(M+H)^+$.

Example 49C

6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane bis(4-methylbenzenesulfonate)

The product from Example 49B (40 mg, 0.12 mmol) in EtOAc (3 mL) was treated with p-toluenesulfonic acid•monohydrate (59 mg, 0.31 mmol). The solution was refluxed for 2 hours and allowed to cool to ambient temperature resulting in formation of

a precipitate. The precipitate was triturated with diethyl ether (2X) and placed under high vacuum to provide 70 mg (85%) of the title compound as a white solid. ^{1}H NMR (D_2O) δ 1.92 (m, 1H), 2.14-2.28 (m, 3H), 2.99 (s, 6H), 2.99 (dt, J=5.5, 12.9 Hz, 1H), 3.31 (dd, J=6.6, 13.4 Hz, 1H), 3.56 (d, J=12.1 Hz, 1H), 3.77 (dd, J=4.4, 12.1 Hz, 1H), 4.38 (m, 2H), 7.25 (dd, J=3.2, 9.0 Hz, 1H), 7.36 (d, J=8.5 Hz, 4H), 7.40 (d, J=9.2 Hz, 1H), 7.68 (d, J=8.5 Hz, 4H), 7.78 (d, J=2.9 Hz, 1H); MS (CI/NH3) m/z 224, 226 $(M+H)^+$; Anal. Calcd for $C_{11}H_{14}ClN_3 \cdot 2.5C_7H_8O_3S \cdot 0.5\ H_2O$: C, 51.61; H, 5.32; N, 6.34. Found: C, 51.31; H, 5.43; N, 6.21.

Example 50

(1R,4R)-2-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

Example 50A

tert-butyl (1R,4R)-5-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 44A was processed according to the procedure described in Example 38A to provide the title compound. MS (DCI/NH_3) m/z 319 $(M+H)^+$.

Example 50B

(1R,4R)-2-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane bis(4-methylbenzenesulfonate)

The product from Example 50A was processed as described in Example 2B to provide the title compound. ^{1}H NMR (MeOD, 300 MHz) δ 2.26 (d, J=12.0 Hz, 1H), 2.25 (d, J=12.0 Hz, 1H), 3.41-3.52 (m, 3H), 3.82 (dd, J=2.0, 10.0 Hz, 1H), 4.65 (t, J=1.0 Hz, 1H), 5.96 (s, 1H), 8.14 (dd, J=1.0, 3.0 Hz,1H), 8.32 (d, J=2.0 Hz, 1H), 8.47 (d, J=1.0 Hz, 1H); MS (DCI/NH_3) m/z 219 $(M+H)^+$; Anal. calculated for $C_{24}H_{30}N_4O_7S_2 \cdot 0.40$ TsOH•1.0 H_2O: C, 50.49; H, 5.57; N, 8.79. Found C, 50.53; H, 5.75; N, 8.76.

Example 51

(1R,4R)-2-(6-chloro-5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 51A

5-bromo-2-chloro-3-methoxypyridine

The product from Example 40B (1.2 g, 5.8 mmol) in diethyl ether (5 mL) was added to a suspension of NaH (181 mg, 7.5 mmol) in dry DMF (30 mL) and diethyl ether (6 mL). After stirring at ambient temperature for 30 minutes, the mixture was treated with a solution of iodomethane (1.06 g, 7.5 mmol) in diethyl ether (3 mL) and stirring was continued for an additional 30 minutes. The reaction mixture was quenched with water (20 mL), extracted with diethyl ether (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on SiO_2 (ethyl acetate/hexane, 1/4) to provide the title compound (0.32 g, 25%) as a colorless oil. MS(DCI/NH_3) m/z 222/224/226 $(M+H)^+$.

Example 51B

tert-butyl (1R,4R)-5-(6-chloro-5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and the product from Example 51A were processed as described in Example 15C to provide the title compound (74 % yield). MS(DCI/NH_3) m/z 340 $(M+H)^+$.

Example 51C

(1R,4R)-2-(6-chloro-5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 51B was processed as described in Example 2B to provide the title compound (50 % yield). ^1H NMR (MeOD, 300 MHz) δ 1.82 (d, J=12.0 Hz, 1H), 1.96 (d, J=12.0 Hz, 1H), 2.97 (s, 3H), 3.58 (dd, J=3.0, 12.0 Hz, 1H), 3.78-3.82 (m, 2H), 3.89 (s, 1H), 4.46 (s, 1H), 4.79 (s, 1H), 6.68 (d, J=2.0 Hz, 1H), 7.28 (d, J=2.0 Hz, 1H); MS (DCI/NH_3) m/z 240 $(M+H)^+$; Anal. calculated for $C_{18}H_{22}N_3O_4SCl \cdot 0.25$ TsOH•0.60 H_2O: C, 50.93; H, 5.45; N, 9.02. Found C, 50.94; H, 5.57; N, 8.95.

Example 52

(1S,4S)-2-(5-pyrimidinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

Example 52A

tert-butyl (1S,4S)-5-(5-pyrimidinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (330 mg, 1.6 mmol), prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), and 5-bromopyrimidine (purchased from Acros Scientific) were processed as described in Example 15C to provide the title compound (99 % yield). MS(DCI/NH_3) m/z 277 $(M+H)^+$.

Example 52B

(1S,4S)-2-(5-pyrimidinyl)-2,5-diazabicyclo[2.2.1]heptane 4-methylbenzenesulfonate

The product from Example 52B was processed as described in Example 2B to provide the title compound (33 % yield). ^1H NMR (MeOD, 300 MHz) δ 1.87-2.01 (m, 2H), 3.01-3.16 (m, 3H), 3.67 (dd, J=2.0, 8.0 Hz, 1H), 3.79 (s, 1H), 4.37 (s, 1H), 8.06 (s, 2H), 8.57 (s, 1H); MS (DCI/NH_3) m/z 177 $(M+H)^+$; Anal. calculated for $C_{16}H_{20}N_4O_3S \cdot 0.10$ TsOH$\cdot 0.25$ H_2O: C, 54.19; H, 5.80; N, 15.14. Found C, 54.24; H, 5.89; N, 15.17.

Example 53

(1S,4S)-2-(3-quinolinyl)-2,5-diazabicyclo[2.2.1]heptane acetate

Example 53A

tert-butyl (1S,4S)-5-(3-quinolinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611), and 3-bromoquinoline (purchased

from the Aldrich Chemical Co.) were coupled according to the procedure described in Example 1A to provide the title compound.

Example 53B

(1S,4S)-2-(3-quinolinyl)-2,5-diazabicyclo[2.2.1]heptane acetate

The product from Example 53A was processed as described in Example 34B to provide the crude hydrochloride. The crude hydrochloride was purified by preparative HPLC (Waters Nova-Pak HR C18 6 μm 60Å 25x100 mm, 0-95% CH_3CN/10 mM NH_4OAc over 10 minutes at 40 mL/minute) to provide the title compound after removal of solvents under reduced pressure. ^1H NMR (MeOD, 300 MHz) δ 1.90 (s, 3H), 2.06 (br d, J=11 Hz, 1H), 2.24 (br d, J=11 Hz, 1H), 3.30, (br s, 2H), 3.41 (d, J=10 Hz, 1H), 3.84 (d, J=10 Hz, 1H), 4.33 (br s, 1H), 4.80 (br s, 1H), 7.34 (m, 1H), 7.46 (m, 2H), 7.73 (br d, J=7 Hz, 1H), 7.87 (br d, J=7 Hz, 1H), 8.51 (br d, J=3 Hz, 1H).

Example 54

(1S,4S)-2-(3-methyl-5-isothiazolyl)-2,5-diazabicyclo[2.2.1]heptane acetate

Example 54A

tert-butyl (1S,4S)-5-(3-methyl-5-isothiazolyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

tert-Butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, prepared as described in (J. Med. Chem., (1988) 31, 1598-1611) and 5-bromo-3-methylisothiazole, prepared as described in (US 3,840,665) were coupled according to the procedure described in Example 1A to provide the title compound.

Example 54B

(1S,4S)-2-(3-methyl-5-isothiazolyl)-2,5-diazabicyclo[2.2.1]heptane acetate

The product from Example 54A was processed as described in Example 53B to provide the title compound. ^{1}H NMR (MeOD, 300 MHz) δ 1.84(s, 3H), 1.86 (m, 1H), 2.04 (br d, J=11 Hz, 1H), 2.18 (s, 3H), 3.06 (m, 2H), 3.16 (br d, J=10 Hz, 1H), 3.30 (m, 1H), 4.05 (br s, 1H), 4.17 (br s, 1H), 5.99 (s, 1H).

Example 55

(1R,4R)-2-(thieno[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane acetate

Example 55A

tert-butyl (1R,4R)-5-(thieno[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The product from Example 15B and 2-bromothieno[3,2-b]pyridine, prepared as described in (J. Het. Chem. (1984), 785-789), were processed as described in Example 1A to provide the title compound.

Example 55B

(1R,4R)-2-(thieno[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane acetate

The product from Example 55A was processed as described in Example 53B to provide the title compound. ^{1}H NMR (MeOD, 300 MHz) δ 1.92 (s, 3H), 2.04 (br d, J=11 Hz, 1H), 2.26 (br d, J=11 Hz, 1H), 3.28 (m, 1H), 3.41 (m, 2H), 3.74 (dd, J=10, 2 Hz, 1H), 4.33 (br s, 1H), 4.53 (br s, 1H), 6.18 (s, 1H), 7.01 (dd, J=8, 4 Hz, 1H), 8.01 (br d, J=8 Hz, 1H), 8.29 (br d, J=4 Hz, 1H).

Example 56

9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane fumarate

Example 56A

tert-butyl 9-methyl-3,9-diazabicyclo[4.2.1]nonane-3-carboxylate

9-Methyl-3,9-diazabicyclo[4.2.1]nonane (4.60 g, 33 mmol), prepared as described in (US 2,999,091), in $CHCl_3$ (50 mL) at 0 °C, was treated with triethyl amine (6.7 g, 66 mmol) and di-t-butyl dicarbonate (14.4 g, 66 mmol). The mixture was allowed to warm to ambient temperature and and stir for 12 hours. The reaction mixture was washed in succession with saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to provide the title compound (99% yield). MS (DCI/NH_3) m/z 241 $(M+H)^+$.

Example 56B

t-butyl 3,9-diazabicyclo[4.2.1]nonane-3-carboxylate

The product of Example 56A was processed (on 33 mmol scale) according to the procedure of Example 36 to provide the title compound (51% yield). MS (DCI/NH_3) m/z 227 $(M+H)^+$, 241 $(M+NH_4)^+$.

Example 56C

t-butyl 9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane-3-carboxylate

The product of Example 56B (17 mmol) and 2-chloro-5-iodopyridine (21 mmol) were coupled according the procedure of Example 15C to provide the title compound (21% yield). MS (DCI/NH_3) m/z 338 $(M+H)^+$, 355 $(M+NH_4)^+$.

Example 56D

9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane

fumarate

The product of Example 56C was treated with trifluoroacetic acid according to the procedure of Example 15D. After purification by chromatography (SiO_2; 10% MeOH:89% CH_2Cl_2:1% NH_4OH), the free base was combined with fumaric acid (1.1 eq.) in hot EtOAc. Upon cooling, the title compound separated as a solid in 97% yield. ^1H NMR (CD_3OD, 300 MHz) δ 1.84-2.08 (m, 3H), 2.22-2.56 (m, 3H), 2.92-3.02 (m, 1H), 3.16-3.29 (m, 2H), 3.58 (d, J=4.5, 13.5 Hz, 1H), 4.47-4.55 (m, 1H), 4.57-4.66 (m, 1H), 6.67 (s, 2H), 7.25 (s, 2H), 7.86 (s, 1H); MS (DCI/NH_3) m/z 238 $(M+H)^+$, 255 $(M+NH_4)^+$;

Anal. Calcd for $C_{12}H_{16}ClN_3 \cdot C_4H_4O_4$: C, 54.32; H, 5.70; N, 11.88. Found: C, 54.33; H, 5.77; N, 11.77.

Example 57

3-(3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane bis(4-methylbenzenesulfonate)

Example 57A

3-(3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane

3,7-Diazabicyclo[3.3.1]nonane, prepared as described in (Garrison, G.L. et. al., J. Org. Chem. 58, 27, (1993) 7670), and 3-bromopyridine were processed as described in Example 1A. The proportions of reagents were changed from Example 1A to the following: $Pd_2(dba)_3$ (0.02 eq), BINAP (0.05 eq), and NaOt-Bu (1.7 eq). The title compound was obtained in 25% yield after purification by flash chromatography (silica gel; $CHCl_3$:MeOH:NH_4OH; 90:5:1). MS (DCI/NH_3) m/z 204 $(M+H)^+$.

Example 57B

3-(3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane bis(4-methylbenzenesulfonate)

The product from Example 57A was treated with p-toluenesulfonic acid (2.0 eq) and the obtained solid recrystallized from ethanol/ether to provide the title compound (53% yield). ^{1}H NMR (CD_3OD, 300MHz) δ 2.04 (m, 2H), 2.37 (s, 6H), 2.39 (m, 2H), 3.23 (m, 2H), 3.31 (m, 2H), 3.59 (bd, J=13.24 Hz, 2H), 4.04 (bd, 12.14 Hz, 2H), 7.23 (d, J=8.09 Hz, 4H), 7.67(d, J=8.09 Hz, 4H), 7.88 (dd, J=5.52, 8.83 Hz, 1H), 8.20-8.24(m, 2H), 8.50 (d, J=2.57 Hz, 1H); MS (DCI/NH_3) m/z 204 $(M+H)^+$; Anal. calculated for $C_{12}H_{17}N_3 \cdot 2.2\ TsOH \cdot H_2O$ C, 56.01; H, 6.04; N, 7.15. Found C, 56.25; H, 6.10; N, 6.79.

Example 58

3-(6-Chloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane 4-methylbenzenesulfonate

Example 58A

3-(6-Chloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane

3,7-Diazabicyclo[3.3.1]nonane, prepared as described in (Garrison, G.L. et. al., J. Org. Chem. 58, 27, (1993) 7670), and 2-chloro-5-iodopyridine were processed as described in Example 57A. The crude was purified by flash chromatography (silica gel; $CHCl_3$:MeOH:NH_4OH; 90:5:1) to provide the title compound (10% yield). MS (DCI/NH_3) m/z 238 $(M+H)^+$.

Example 58B

3-(6-Chloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane

4-methylbenzenesulfonate

The product of Example 58A was treated with p-toluenesulfonic acid (1.0 eq) and the obtained solid recrystallized from ethanol/ether to provide the title compound (53% yield) ^{1}H NMR (CD_3OD, 300 MHz) δ 2.00 (m, 2H), 2.31 (bs, 2H), 2.37 (s, 3H), 3.10 (m, 2H), 3.35 (m,2H), 3.57 (bd, J=13.22 Hz, 2H), 3.85 (bd, 11.19 Hz, 2H), 7.23 (d, J=8.14 Hz, 2H), 7.34 (d, J=8.13 Hz, 1H), 7.57 (dd, J=3.05, 8.81 Hz, 1H), 7.70 (d, J = 8.13 Hz, 2H), 8.15 (d, J=3.39 Hz, 1H); MS (DCI/NH_3) m/z 238 $(M+H)^+$; Anal. calculated for $C_{12}H_{16}ClN_3 \cdot 1.1$ TsOH$\cdot 0.5$ H_2O C, 54.25; H, 5.96; N, 9.63. Found C, 54.05; H, 5.60; N, 9.61.

Example 59

6-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane

Example 59A

2-[(2-nitrophenyl)sulfonyl]-2-azabicyclo[2.2.1]hept-5-ene

2-Azabicyclo[2.2.1]hept-5-ene (52.5 g, 54 mmole), prepared as described in (J Am Chem. Soc., (1985) 107, 1768), 2-nitrobenzenesulfonyl chloride (119.6 , 54 mmole), and triethylamine (75 mL, 0.54 mmole) were combined in methylene chloride (500 mL) under a nitrogen atmosphere and stirred for 16 hours. The reaction mixture was quenched with water (500 mL) and the phases separated. The organic phase was washed with 2M HCl (5 x 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

The residue was purified by chromatography on silica gel (chloroform then hexane:EtOAc 95:5 to 8:2) to provide the title compound (23 g, 23% yield). MS (DCI/NH_3) m/e 281 $(M+H)^+$, 298 $(M+NH_4)^+$.

Example 59B

3-benzyl-6-[(2-nitrophenyl)sulfonyl]-3,6-diazabicyclo[3.2.1]octane

Ozone (O_3/O_2) was bubbled through a solution of the product from Example 59A (5.6 g, 2 mmol) in methanol (100 mL) at -78 °C. After one hour, a stream of oxygen was bubbled through the reaction mixture to remove excess ozone. The mixture was treated with dimethyl sulfide (2 mL) and the reaction mixture was allowed to warm to ambient temperature. After 30 minutes, benzylamine hydrochloride (25 g, 170 mmol) and 3A molecular sieves (30g) were added. After 2 hours, $NaBH_3CN$ (6.3 g, 10 mmol) was added and the reaction mixture stirred for an additional 16 hours. The solids were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was diluted with water (150 mL), acidified with 6N HCl (200 mL), and allowed to stir for 16 hours. Solid NaOH was added to bring the mixture to pH ~13. The mixture was extracted with EtOAc (5x 200 mL). The extracts were combined, dried (K_2CO_3), and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$:MeOH 100:0 to 95:5) to provide the title compound (2.0 g, 28% yield). MS (DCI/NH_3) m/e 288 $(M+H)^+$.

Example 59C

3-benzyl-3,6-diazabicyclo[3.2.1]octane

The product of Example 59B (1.98g, 5 mmole) in DMF (5 mL) was treated with mercaptoacetic acid (0.7 ml, 10 mmole) and lithium hydroxide (0.48g, 20 mmole). After stirring under a nitrogen atmosphere for 2 hours, the reaction mixture was poured into saturated Na_2CO_3 (20 mL) and extracted with EtOAc (5 x 20mL). The organic extracts were combined, dried (K_2CO_3), and concentrated under reduced pressure. The residue was purified on silica gel ($CHCl_3$:MeOH:NH_4OH 95:5:0 to 9:1:0.1) to provide the title compound (450 mg, 45% yield). MS (DCI/NH_3) m/e 203 $(M+H)^+$.

Example 59D

3-benzyl-6-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane

The product of Example 59C (290 mg, 1.4 mmole) and 3-bromopyridine (340 mg, 2.15 mmole) were coupled using the procedure of Example 1A to provide the title compound (306 mg, 90% yield). MS (DCI/NH_3) m/e 280 $(M+H)^+$.

Example 59E

6-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane

The product from Example 59D (290 mg, 1.1 mmole), in ethanol (2.9 mL) was treated with 20% $Pd(OH)_2/C$ (117 mg) under a hydrogen atmosphere (60 psi) for 36 hours. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was purified by chromatography (SiO_2, $CHCl_3$:MeOH:NH_4OH, 9:1:0 to 9:1:0.1) to provide the title compound (42 mg, 21% yield). ^1H NMR (CD_3OD, 300 MHz) δ 2.17 (br s, 1H), 2.91 (br s, 1H),3.40-3.70 (m, 8H) 4.51 (m, 1H), 7.84-7.85 (m, 2H), 8.09 (m, 1H), 8.19 (br s, 1H); MS (DCI/NH_3) m/e 190 $(M+H)^+$.

Example 60

3-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane

bis(4-methylbenzenesulfonate)

Example 60A

t-butyl 3-benzyl-3,6-diazabicyclo[3.2.1]octane-6-carboxylate

The product of Example 59C can be treated with di-t-butyl dicarbonate (1.1 eq.) in methylene chloride for 4 hours. The solvent is removed under reduced pressure and the residue purified by chromatography to provide the title compound.

Example 60B

t-butyl 3,6-diazabicyclo[3.2.1]octane-6-carboxylate

The product from Example 60A can be processed according to the procedure of Example 59E to provide the title compound.

Example 60C

3-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane

bis(4-methylbenzenesulfonate)

The product from Example 60B can be processed according to the procedure of Example 2B to provide the title compound.

In Vitro Data

Determination of Nicotinic Acetylcholine Receptor Binding Potencies

Compounds of the invention were subjected to in vitro assays against the nicotinic acetylcholine receptor as described below and were found to be effective binders to the receptor. The In Vitro protocols for determination of nicotinic acetylcholine channel receptor binding potencies of ligands were determined as follows.

Binding of [^{3}H]-cytisine ([^{3}H]-CYT) to neuronal nicotinic acetylcholine receptors was accomplished using crude synaptic membrane preparations from whole rat brain (Pabreza et al., Molecular Pharmacol., 1990, 39:9). Washed membranes were stored at -80 °C prior to use. Frozen aliquots were slowly thawed and resuspended in 20 volumes of buffer (containing: 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$ and 50 mM Tris-Cl, pH 7.4 @4 °C). After centrifuging at 20,000x g for 15 minutes, the pellets were resuspended in 30 volumes of buffer.

The test compounds were dissolved in water to make 10 mM stock solutions. Each solution was then diluted (1:100) with buffer (as above) and further taken through seven serial log dilutions to produce test solutions from 10^{-5} to 10^{-11} M.

Homogenate (containing 125-150 µg protein) was added to triplicate tubes containing the range of concentrations of test compound described above and [^{3}H]-CYT (1.25 nM) in a final volume of 500 µL. Samples were incubated for 60 minutes at 4 °C, then rapidly filtered through Whatman GF/B filters presoaked in 0.5% polyethyleneimine using 3 x 4 mL of ice-cold buffer. The filters are counted in 4 mL of Ecolume® (ICN). Nonspecific binding was determined in the presence of 10 µM (-)-nicotine and values were expressed as a percentage of total binding. IC_{50} values were determined with the RS-1 (BBN) nonlinear least squares curve-fitting program and IC_{50} values were converted to Ki values using the Cheng and Prusoff correction ($K_i=IC_{50}/(1+[ligand]/Kd$

of ligand).

The results are detailed in Table 1. Each Example Number corresponds to the synthetic Examples described above. Examples 1-17 and 20-59 are compounds of the present invention. Examples 18 and 19 are comparative. Example 18 is the 6-chloro-2-pyridinyl [2.2.1]derivative, corresponding to Example 1, the 6-chloro-3-pyridinyl derivative; and Example 19 is the 6-chloro-2-pyridinyl[3.2.1] derivative, corresponding to Example 12, the 6-chloro-3-pyridinyl[3.2.1]derivative. As a lower K_i value is more desirable, the binding data suggest that the 3-pyridinyl derivative compounds of the present invention have higher affinity for the neuronal nicotinic acetylcholine receptor than 2-pyridinyl derivative compounds.

Table 1

Binding Data

Example Number	Average K_i (nM)
1	0.041
2	6.0
3	20
4	3.8
5	65
6	22
7	1900
8	2600
9	>10,000
10	37
11	37
12	93
13	0.41
14	11

15	0.01
16	24
17	0.063
18	400
19	>10,000
20	52
21	0.33
22	4.1
23	1.6
24	0.012
25	0.40
27	0.05
28	109
29	37
30	0.17
31	1.2
32	1.6
33	0.03
34	140
35	1.5
36	0.06
37	0.55
38	24
39	0.04
40	0.17
41	0.03

42	0.02
43	0.57
44	0.03
45	1.6
46	0.25
47	0.009
48	0.01
49	2.7
50	0.83
51	0.10
52	1.0
53	17
54	5.0
55	0.84
56	0.21
57	0.02
58	0.02
59	2.2

In Vivo Data

Determination of Effectiveness of Nicotinic Acetylcholine Receptor Ligands as Analgesic Agents in the Mouse Hot Plate Paradigm

An in vivo protocol was utilized to determine the effectiveness of nicotinic acetylcholine receptor ligands as analgesic agents in the mouse hot plate paradigm.

Separate groups of mice, (n=8/group) were utilized for each dose group. All drugs were administered by the intraperitoneal route of administration. Test drugs were dissolved in water to make a 6.2 mM stock solution. Animals were dosed with this solution (10 mL/kg body weight) for a 62 micromol/kg dose. Lower doses were

administered similarly, following serial dilution of the stock solution in half-log increments. Animals were dosed 30 minutes prior to testing in the hot plate. The hot-plate utilized was an automated analgesia monitor (Model #AHP16AN, Omnitech Electronics, Inc. of Columbus, Ohio). The temperature of the hot plate was maintained at 55 °C and a cut-off time of 180 seconds was utilized. Latency until the tenth jump was recorded as the dependent measure. An increase in the tenth jump latency relative to the control was considered an effect.

Table 2 shows the minimally effective dose (MED), among the doses tested, at which a significant effect, as defined above, was observed for the present compounds. The data shows that selected compounds of the invention show a significant antinociceptive effect at doses ranging from 0.62 to 62 μmol/kg.

Table 2

Mouse Hot Plate Data

Example Number	(MED) μmol/kg
1	6.2
4	62
15	0.62
16	6.2
20	62
22	19
23	62
24	6.2
25	19
27	1.9
30	1.9
31	62
33	0.19
35	19
36	1.9

37	6.2
38	19
39	62
40	19
41	6.2
44	0.62
46	6.2
47	6.2
48	6.2
57	1.9
58	0.62

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which can be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) which is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. Alternatively, the compound can be administered as a pharmaceutical composition

containing the compound of interest in combination with one or more pharmaceutically acceptable excipients. The phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.001 to about 1000 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range of from about 0.001 to about 5 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

The present invention also provides pharmaceutical compositions that comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be specially formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally , intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration

which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), vegetable oils (such as olive oil), injectable organic esters (such as ethyl oleate) and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared

by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are natural and synthetic phospholipids and phosphatidyl cholines (lecithins) used separately or together.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed.,

Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Compounds of the present invention that are formed by in vivo conversion of a different compound that was administered to a mammal are intended to be included within the scope of the present invention.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms, such as hemi-hydrates. In general, the solvated forms, with pharmaceutically acceptable solvents such as water and ethanol among others are equivalent to the unsolvated forms for the purposes of the invention.

The present compounds may have activity against disorders which are mediated through the central nervous system. The following references describe various disorders affected by nicotinic acetylcholine receptors: 1) Williams, M.; Arneric, S. P.: Beyond the Tobacco Debate: dissecting out the therapeutic potential of nicotine. Exp. Opin. Invest. Drugs (1996)5(8): 1035-1045; 2) Arneric, S. P.; Sullivan, J. P.; Williams, W.: Neuronal nicotinic acetylcholine receptors. Novel targets for central nervous system theraputics. In: Psychopharmacology: The Fourth Generation of Progress. Bloom FE, Kupfer DJ (Eds.), Raven Press, New York (1995): 95-109; 3) Arneric, S. P.; Holladay, M. W.; Sullivan, J. P.: Cholinergic channel modulators as a novel therapeutic strategy for Alzheimer's disease. Exp. Opin. Invest. Drugs (1996) 5(1): 79-100; 4) Lindstrom, J.: Nicotinic Acetylchloline Receptors in Health and Disease. Molecular Neurobiology (1997) 15: 193-222; and 5) Lloyd, G K; Menzaghi, F; Bontempi B; Suto, C; Siegel, R; Akong, M; Stauderman, K; Velicelebi, G; Johnson, E; Harpold, M M; Rao, T S; Sacaan, A I; Chavez-Noriega, L E; Washburn, M S; Vernier, J M; Cosford, N D P; McDonald, L A: The potential of subtype-selective neuronal nicotinic acetylcholine receptor agonists as therapeutic agents. Life Sciences (1998)62(17/18): 1601-1606. These disorders include, but are not limited to the following: pain (references 1 and 2), Alzheimer's disease (references 1-5), Parkinson's disease (references 1, 4 and 5), memory dysfunction, Tourette's syndrome (references 1, 2 and 4), sleep disorders (reference 1), attention deficit hyperactivity disorder (references 1 and 3), neurodegeneration, inflammation, neuroprotection (references 2 and 3), amyotrophic atral sclerosis, anxiety (references 1, 2 and 3), depression (reference 2), mania,

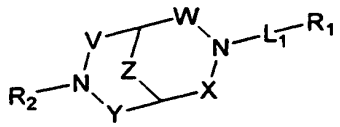
schizophrenia (references 1, 2 and 4), anorexia and other eating disorders, AIDS-induced dementia, epilepsy (references 1,2 and 4), urinary incontinence (reference 1), Crohn's disease, migraines, PMS, erectile disfunction, substance abuse, smoking cessation (references 1 and 2) and inflammatory bowel syndrome (references 1 and 4) among others.

The present invention is illustrated by way of the foregoing description and examples. The foregoing description is intended as a non-limiting illustration, since many variations will become apparent to those skilled in the art in view thereof. It is intended that all such variations within the scope and spirit of the appended claims be embraced thereby.

Changes can be made in the composition, operation and arrangement of the method of the present invention described herein without departing from the concept and scope of the invention as defined in the following claims:

WE CLAIM:

1. A compound of formula I



I,

or a pharmaceutically acceptable salt thereof wherein:

V is selected from the group consisting of a covalent bond and CH_2;

W is selected from the group consisting of a covalent bond, CH_2, and CH_2CH_2;

X is selected from the group consisting of a covalent bond and CH_2;

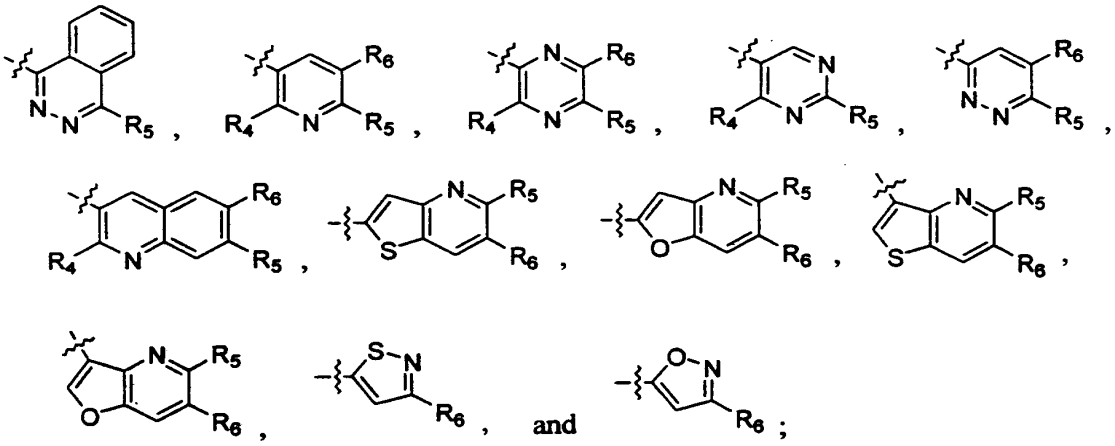
Y is selected from the group consisting of a covalent bond, CH_2, and CH_2CH_2;

Z is selected from the group consisting of CH_2, CH_2CH_2, and $CH_2CH_2CH_2$;

L_1 is selected from the group consisting of a covalent bond and $(CH_2)_n$;

n is 1-5;

R_1 is selected from the group consisting of



and

;

R_2 is selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, aminoalkyl, aminocarbonylalkyl, benzyloxycarbonyl, cyanoalkyl, dihydro-3-pyridinylcarbonyl, hydroxy, hydroxyalkyl, phenoxycarbonyl, and $-NH_2$;

R_4 is selected from the group consisting of hydrogen, alkyl, and halogen;

R_5 is selected from the group consisting of hydrogen, alkoxy, alkyl, halogen, nitro, and $-NH_2$;

R_6 is selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, mercapto, mercaptoalkyl, nitro, 5-tetrazolyl, $-NR_7SO_2R_8$, $-C(NR_7)NR_7R_8$, $-CH_2C(NR_7)NR_7R_8$, $-C(NOR_7)R_8$, $-C(NCN)R_7$, $-C(NNR_7R_8)R_8$, $-S(O)_2OR_7$, and $-S(O)_2R_7$; and .

R_7 and R_8 are independently selected from the group consisting of hydrogen and alkyl;

with the proviso that the following compounds are excluded,

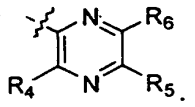
3-(6-chloro-3-pyridazinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-chloro-2-pyrazinyl)-3,8-diazabicyclo[3.2.1]octane;

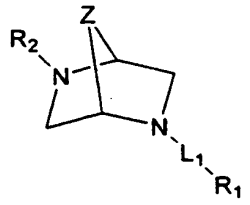
8-(6-chloro-3-pyridazinyl)-3,8-diazabicyclo[3.2.1]octane; and

8-(6-chloro-2-pyrazinyl)-3,8-diazabicyclo[3.2.1]octane; and

with the further proviso that when V and X are each a covalent bond; W, Y, and Z are each CH_2; and L_1 is a covalent bond; then R_1 is other than



2. A compound according to claim 1 of formula II



II,

or a pharmaceutically acceptable salt thereof wherein:

Z is selected from the group consisting of CH_2 and CH_2CH_2.

3. A compound according to claim 2 selected from the group consisting of:

(1S,4S)-2-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methyl-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(4-chloro-1-phthalazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(4-chloro-1-phthalazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-methoxycarbonyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-pyrimidinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(3-quinolinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(3-methyl-5-isothiazolyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(thieno[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane; and

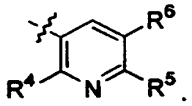
(1S,4S)-2-(furo[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane.

4. A compound according to claim 2 wherein:

Z is CH_2;

L_1 is a covalent bond; and

R_1 is



5. A compound according to claim 4 selected from the group consisting of:

(1S,4S)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-amino-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-[5-(benzyloxy)-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-[5-hydroxy-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-nitro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-chloro-3-pyridinyl)-5-cyanomethyl-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-chloro-5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5,6-dichloro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-chloro-5-cyano-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-methoxy-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-bromo-6-chloro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-cyano-6-chloro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-hydroxymethyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane; (1S,4S)-2-(5-hydroxymethyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-hydroxymethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-aminomethyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-aminomethyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-carboxy-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-carboxy-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1S,4S)-2-(5-carboxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminocarbonyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminocarbonyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-chloro-5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(6-fluoro-5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(2-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-methyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminosulfonyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1S,4S)-2-(5-aminosulfonyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane; and

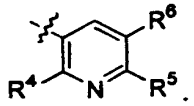
(1S,4S)-2-(5-aminosulfonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane.

6. A compound according to claim 2 wherein:

Z is CH_2CH_2;

L_1 is a covalent bond; and

R_1 is



7. A compound according to claim 6 selected from the group consisting of:

(1S,4S)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

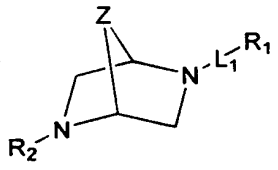
(1S,4S)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(6-chloro-5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1S,4S)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1S,4S)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1S,4S)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1S,4S)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1S,4S)-2-(5-bromo-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;
(1S,4S)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane; and
(1S,4S)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane.

8. A compound according to claim 1 of formula III



III,

or a pharmaceutically acceptable salt wherein:
Z is selected from the group consisting of CH_2 and CH_2CH_2.

9. A compound according to claim 8 selected from the group consisting of:
(1R,4R)-2-(6-chloro-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(thieno[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(furo[3,2-b]pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(6-chloro-5-methyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(6-chloro-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(6-chloro-5-methyl-3-pyridazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(4-chloro-1-phthalazinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(4-chloro-1-phthalazinyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(6-chloro-5-methoxycarbonyl-3-pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane;
(1R,4R)-2-(5-pyrimidinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(3-quinolinyl)-2,5-diazabicyclo[2.2.1]heptane; and

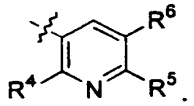
(1R,4R)-2-(3-methyl-5-isothiazolyl)-2,5-diazabicyclo[2.2.1]heptane.

10. A compound according to claim 8 wherein:

Z is CH_2;

L_1 is a covalent bond; and

R_1 is



11. A compound according to claim 10 selected from the group consisting of:

(1R,4R)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-3-pyridinyl)-5-cyanomethyl-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-nitro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-bromo-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-amino-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-[5-(benzyloxy)-3-pyridinyl]-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-cyano-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-bromo-6-chloro-3-pyridinyl)-2,5diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-cyano-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxymethyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxymethyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxymethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminomethyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminomethyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-carboxy-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-carboxy-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-carboxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminocarbonyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminocarbonyl-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-chloro-5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(6-fluoro-5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-hydroxyiminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(2-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-methyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminosulfonyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane;

(1R,4R)-2-(5-aminosulfonyl-6-chloro-3-pyridinyl)-2,5-

diazabicyclo[2.2.1]heptane; and

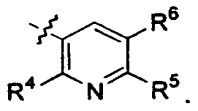
(1R,4R)-2-(5-aminosulfonyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane.

12. A compound according to claim 8 wherein:

Z is CH_2CH_2;

L_1 is a covalent bond; and

R_1 is



13. A compound according to claim 12 selected from the group consisting of:

(1R,4R)-2-(6-chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(5,6-dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(6-chloro-5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(5-methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(5-bromo-6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane;

(1R,4R)-2-(3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane; and

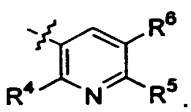
(1R,4R)-2-(6-chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.2]octane.

14. A compound according to claim 8 wherein:

Z is CH_2;

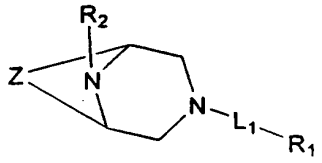
L_1 is $(CH_2)_q$; and

R_1 is



15. A compound according to claim 14 that is (1R,4R)-2-(3-pyridinylmethyl)-2,5-diazabicyclo[2.2.1]heptane.

16. A compound according to claim 1 of formula IV



IV,

or a pharmaceutically acceptable salt thereof wherein:

Z is selected from the group consisting of CH_2CH_2 and $CH_2CH_2CH_2$.

17. A compound according to claim 16 wherein Z is CH_2CH_2.

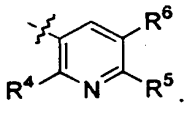
18. A compound according to claim 17 that is 3-(3-pyridazinyl)-3,8-diazabicyclo[3.2.1]octane.

19. A compound according to claim 16 wherein:

Z is CH_2CH_2;

L_1 is a covalent bond; and

R_1 is



20. A compound according to claim 19 selected from the group consisting of:

3-(6-nitro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-amino-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-chloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-chloro-5-methyl-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5,6-dichloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-chloro-5-ethynyl-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-chloro-5-cyano-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-methoxy-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-fluoro-5-methyl-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(6-fluoro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-cyano-6-fluoro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

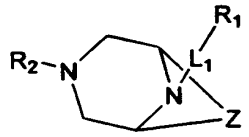
3-(5-bromo-6-chloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-aminomethyl-6-chloro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane;

3-(5-aminomethyl-6-fluoro-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane; and

3-(5-aminomethyl-3-pyridinyl)-3,8-diazabicyclo[3.2.1]octane.

21. A compound according to claim 1 of formula V



V,

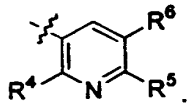
or a pharmaceutically acceptable salt wherein:

Z is selected from the group consisting of CH_2CH_2 and $CH_2CH_2CH_2$.

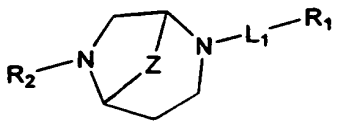
22. A compound according to claim 21 wherein:

L_1 is a covalent bond; and

R_1 is



23. A compound according to claim 1 of formula VI



VI,

or a pharmaceutically acceptable salt wherein:

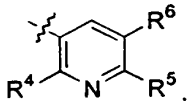
Z is selected from the group consisting of CH_2 and CH_2CH_2.

24. A compound according to claim 23 wherein:

Z is CH_2;

L_1 is a covalent bond; and

R_1 is



25. A compound according to claim 24 selected from the group consisting of:

2-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

2-(3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-chloro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5,6-dichloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-chloro-5-cyano-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5-methoxy-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-2-(5-bromo-6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(6-chloro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(5,6-dichloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(6-chloro-5-ethynyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(6-chloro-5-cyano-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(5-methoxy-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(6-fluoro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

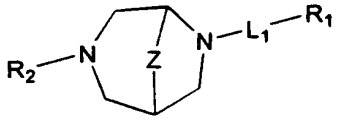
(1R,5S)-2-(6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(5-ethynyl-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-2-(5-cyano-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane; and

(1R,5S)-2-(5-bromo-6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane.

26. A compound according to claim 1 of formula VII



VII,

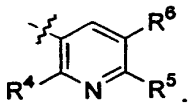
or a pharmaceutically acceptable salt wherein:

Z is selected from the group consisting of CH_2 and CH_2CH_2.

27. A compound according to claim 26 wherein

L_1 is a covalent bond and

R_1 is



28. A compound according to claim 27 selected from the group consisting of:

(1R,5R)-6-(6-chloro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(5,6-dichloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(6-chloro-5-ethynyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(6-chloro-5-cyano-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(5-methoxy-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(6-fluoro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(5-ethynyl-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

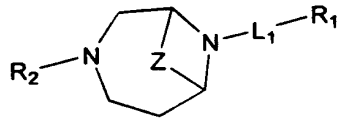
(1R,5R)-6-(5-cyano-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(5-bromo-6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-6-(6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-chloro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(5,6-dichloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-chloro-5-ethynyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-chloro-5-cyano-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(5-methoxy-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-fluoro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(5-ethynyl-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(5-cyano-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(5-bromo-6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1S,5S)-6-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane; and
(1S,5S)-6-(6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane.

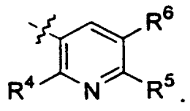
29. A compound according to claim 1 of formula VIII



VIII,

or a pharmaceutically acceptable salt wherein:
Z is selected from the group consisting of CH_2CH_2 and $CH_2CH_2CH_2$.

30. A compound according to claim 29 wherein
Z is CH_2CH_2;
L_1 is a covalent bond; and
R_1 is



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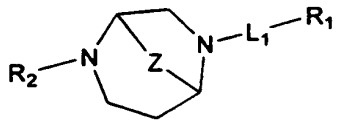
31. A compound according to claim 30 selected from the group consisting of:
9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;

(1R,6S)-9-(6-chloro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(5,6-dichloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(6-chloro-5-ethynyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(6-chloro-5-cyano-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(5-methoxy-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(6-fluoro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(5-ethynyl-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(5-cyano-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(5-bromo-6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-9-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-chloro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5,6-dichloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-chloro-5-ethynyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-chloro-5-cyano-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5-methoxy-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-fluoro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5-ethynyl-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5-cyano-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(5-bromo-6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-9-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane; and
(1S,6R)-9-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane.

32. A compound according to claim 1 of formula IX



IX,

or a pharmaceutically acceptable salt wherein:

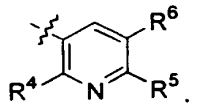
Z is selected from the group consisting of CH_2 and CH_2CH_2.

33. A compound according to claim 32 wherein:

Z is CH_2;

L_1 is a covalent bond; and

R_1 is



34. A compound according to claim 33 selected from the group consisting of:

6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(6-chloro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(5,6-dichloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(6-chloro-5-ethynyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(6-chloro-5-cyano-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(5-methoxy-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(6-fluoro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(5-ethynyl-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(5-cyano-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(5-bromo-6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1R,5S)-6-(3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-6-(6-chloro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-6-(5,6-dichloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-6-(6-chloro-5-ethynyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-6-(6-chloro-5-cyano-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

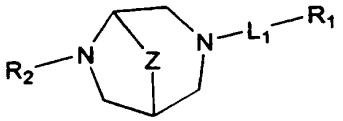
(1S,5R)-6-(5-methoxy-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-6-(6-fluoro-5-methyl-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-6-(6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;

(1S,5R)-6-(5-ethynyl-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(5-cyano-6-fluoro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(5-bromo-6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane;
(1S,5R)-6-(6-chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane; and
(1S,5R)-6-(3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane.

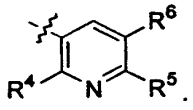
35. A compound according to claim 1 of formula X



X,

or a pharmaceutically acceptable salt wherein:
Z is selected from the group consisting of CH_2 and CH_2CH_2.

36. A compound according to claim 35 wherein
L_1 is a covalent bond and
R_1 is



37. A compound according to claim 36 selected from the group consisting of:
(1R,5R)-3-(6-chloro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5,6-dichloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-chloro-5-ethynyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-chloro-5-cyano-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5-methoxy-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-fluoro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5-cyano-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;
(1R,5R)-3-(5-bromo-6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-3-(6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1R,5R)-3-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(6-chloro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(5,6-dichloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(6-chloro-5-ethynyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(6-chloro-5-cyano-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(5-methoxy-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(6-fluoro-5-methyl-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

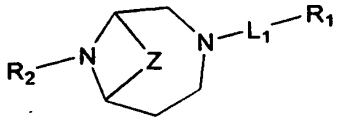
(1S,5S)-3-(5-cyano-6-fluoro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(5-bromo-6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane;

(1S,5S)-3-(6-chloro-3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane; and

(1S,5S)-3-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]octane.

38. A compound according to claim 1 of formula XI



XI,

or a pharmaceutically acceptable salt wherein:

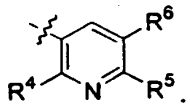
Z is selected from the group consisting of CH_2CH_2 and $CH_2CH_2CH_2$.

39. A compound according to claim 38 wherein

Z is CH_2CH_2;

L_1 is a covalent bond; and

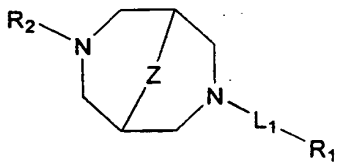
R_1 is



40. A compound according to claim 39 selected from the group consisting of:

3-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
9-methyl-3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(6-chloro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(5,6-dichloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(6-chloro-5-ethynyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(6-chloro-5-cyano-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(5-methoxy-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(6-fluoro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(5-cyano-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(5-bromo-6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1R,6S)-3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(6-chloro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(5,6-dichloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(6-chloro-5-ethynyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(6-chloro-5-cyano-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(5-methoxy-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(6-fluoro-5-methyl-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(5-cyano-6-fluoro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(5-bromo-6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane;
(1S,6R)-3-(6-chloro-3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane; and
(1S,6R)-3-(3-pyridinyl)-3,9-diazabicyclo[4.2.1]nonane.

41. A compound according to claim 1 of formula XII



XII,

or a pharmaceutically acceptable salt wherein:

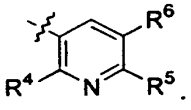
Z is selected from the group consisting of CH_2 and CH_2CH_2.

42. A compound according to claim 41 wherein:

Z is CH_2;

L_1 is a covalent bond; and

R_1 is



43. A compound according to claim 42 selected from the group consisting of:

3-(3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-chloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-chloro-5-methyl-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(5,6-dichloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-chloro-5-ethynyl-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-chloro-5-cyano-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(5-methoxy-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-fluoro-5-methyl-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(6-fluoro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(5-ethynyl-6-fluoro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane;

3-(5-cyano-6-fluoro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane; and

3-(5-bromo-6-chloro-3-pyridinyl)-3,7-diazabicyclo[3.3.1]nonane.

44. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier.

45. A method for selectively controlling neurotransmitter release in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I.

46. A method of treating a disorder in a host mammal in need of such treatment comprising administering a therapeutically effective amount of a compound of formula I.

47. The method of claim 46 wherein the disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, memory dysfunction, Tourette's syndrome, sleep disorders, attention deficit hyperactivity disorder, neurodegeneration, inflammation, neuroprotection, amyotrophic atral sclerosis, anxiety, depression, mania, schizophrenia, anorexia and other eating disorders, AIDS-induced dementia, epilepsy, urinary incontinence, Crohn's disease, migraines, premenstraul syndrome, erectile dysfunction, substance abuse, smoking cessation, and inflammatory bowel syndrome.

48. The method of claim 46 wherein the disorder is pain.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 00/01620

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/08 A61K31/395 A61P25/00 C07D471/08 C07D519/00
//(C07D487/08,209:00,209:00),(C07D487/08,241:00,209:00),
(C07D471/08,221:00,209:00),(C07D487/08,243:00,209:00),
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 54181 A (NEUROSEARCH A/S) 3 December 1998 (1998-12-03) claims 1,6 ---	1,44
A	WO 98 54182 A (NEUROSEARCH A/S) 3 December 1998 (1998-12-03) claims 1,6 ---	1,44
A	US 5 478 939 A (EUGENE TRYBULSKI ET AL.) 26 December 1995 (1995-12-26) cited in the application * complete document * --- -/--	1

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2000	06/07/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 00/01620

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D471/08,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DANIELA BARLOCCO ET AL.: "Mono- and disubstituted-3,8-diazabicyclo(3.2.1)octane derivatives as analgesics structurally related to epibatidine: synthsis, activity, and modeling" JOURNAL OF MEDICINAL CHEMISTRY., vol. 41, no. 5, - 1998 pages 674-681, XP002140147 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 cited in the application page 674	1

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Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2000	

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 00/01620

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0984965 A	15-03-2000
		NO 995850 A	29-11-1999
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		EP 0984966 A	15-03-2000
		ZA 9804640 A	11-12-1998
US 5478939 A	26-12-1995	NONE	

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(71) Applicant *(for all designated States except US)*: PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).

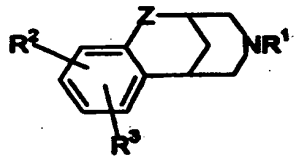
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: COE, Jotham, Wadsworth [US/US]; 8 Bush Hill Drive, Niantic, CT 06357 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS



(I)

(57) Abstract

Compounds of formula (I) and their pharmaceutically acceptable salts, wherein R^1, R^2, R^3 and Z are defined as in the specification, intermediates in the synthesis of such compounds, pharmaceutical compositions containing such compounds and methods of using such compounds in the treatment of neurological and psychological disorders are claimed.

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BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Background of the Invention

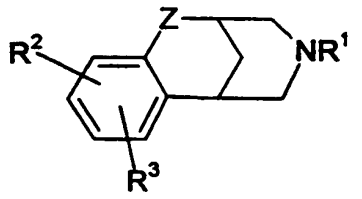
This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

The compounds of this invention may also be used in combination with an antidepressant such as, for example, a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's Chorea or traumatic brain injury (TBI); in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD, stroke, Huntington's Chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD stroke, Huntington's Chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal antiinflammatory agents and estrogen-like therapy.

Other compounds that bind to neuronal nicotinic receptor sites are referred to in United States Patent Application 08/963,852, which was filed on November 4, 1997, and in United States Provisional Patent Application 60/070,245, which was filed on December 31, 1997. Both of the foregoing applications are owned in common with the present application, and both are incorporated herein by reference in their entireties.

Summary of the Invention

This invention relates to aryl fused azapolycyclic compounds of the formula



(I)

wherein Z is CH_2, C(=O) or CF_2;

R^1 is hydrogen, $(C_1$-$C_6)$alkyl, unconjugated $(C_3$-$C_6)$alkenyl, benzyl, $XC(=O)R^{13}$ or $-CH_2CH_2$-O-$(C_1$-$C_4)$alkyl;

R^2 and R^3 are selected independently, from hydrogen, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, hydroxy, nitro, amino, halo, cyano, $-SO_q(C_1$-$C_6)$alkyl wherein q is zero, one or two, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$amino, CO_2R^4, $CONR^5R^6$, $SO_2NR^7R^8$, $C(=O)R^{13}$, $XC(=O)R^{13}$, aryl-$(C_0$-$C_3)$ alkyl or aryl-$(C_0$-$C_3)$alkyl-O- wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0$-$C_3)$alkyl or heteroaryl-$(C_0$-$C_3)$alkyl-O-, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and $X^2(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl, wherein X^2 is absent or X^2 is $(C_1$-$C_6)$alkylamino or $[(C_1$-$C_6)$alkyl$]_2$amino, and wherein the $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl moiety of said $X^2(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl may be optionally substituted with from two to seven fluorine atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-$(C_0$-$C_3)$alkyl and said heteroaryl-$(C_0$-$C_3)$alkyl may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1$-$C_6)$ alkyl optionally substituted with from one to seven fluorine atoms, $(C_1$-$C_6)$ alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), hydroxy, nitro, cyano, amino, $(C_1$-$C_6)$ alkylamino and $[(C_1$-$C_6)$ alkyl$]_2$ amino;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from $(C_0$-$C_6)$

alkoxy-(C_0-C_6)alkyl-, wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, oxo, cyano, halo, hydroxy, amino, (C_1 -C_6)alkylamino, [(C_1 -C_6) alkyl]$_2$amino, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as in the definition of R^2 and R^3 above;

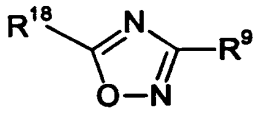
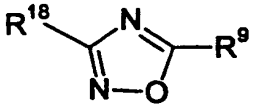
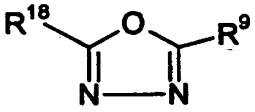
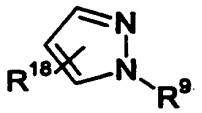
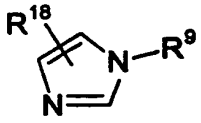
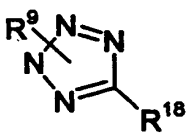
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, -N-(C_1-C_6)alkylpiperizine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1-C_6)alkylene;

with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen; and (c) no fluorine atom in any of the fluoro substituted alkyl or alkoxy moieties of R^2 and R^3 can be attached to a carbon that is attached to a heteroatom;

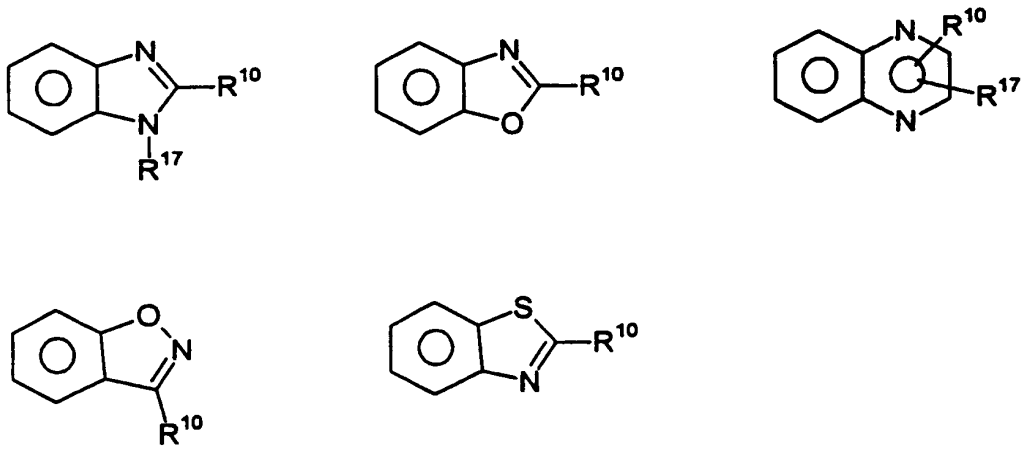
and the pharmaceutically acceptable salts of such compounds.

Examples of heteroaryl groups that each of R^2 and R^3 can be are the following: thienyl, oxazoyl, isoxazolyl, pyridyl, pyrimidyl, thiazolyl, tetrazolyl, isothiazolyl, triazolyl, imidazolyl, tetrazolyl, pyrroyl and the following groups:

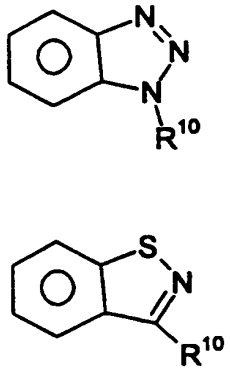
wherein one of R^9 and R^{18} is hydrogen or (C_1 -C_6) alkyl, and the other is a bond to the benzo ring of formula I.

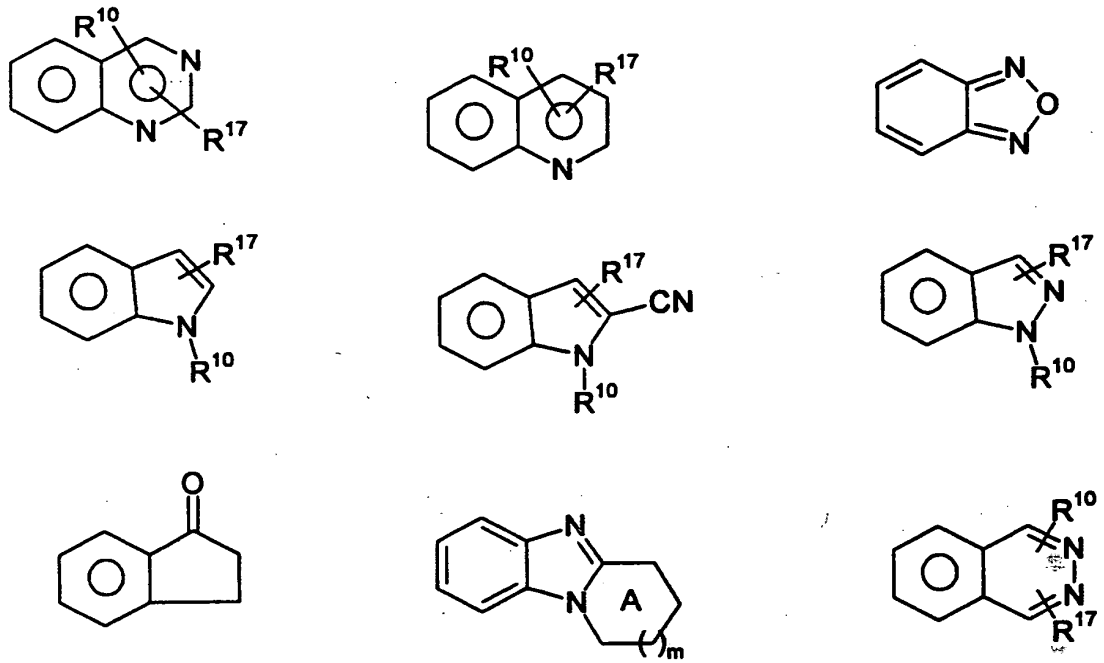
Examples of compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:



wherein R^{10} and R^{17} are selected, independently, from (C_0 -C_6) alkoxy-(C_0-C_6)alkyl wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms, (C_1 -C_6) alkoxy optionally substituted with from one to seven fluorine atoms, nitro, cyano, halo, amino, (C_1 -C_6)alkylamino, [(C_1 -C_6) alkyl]$_2$amino, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as in the definition of R^2 and R^3 above;

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system selected from the following:





wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or -N(C_1-C_6)alkyl.

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein neither R^2 nor R^3 is attached to the benzo ring of formula I via an oxygen atom.

Other embodiments of this invention relate to compounds of the formula I wherein R^1 is not methyl.

Examples of specific compounds of the formula I are the following:

11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;

1-[11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;

1-[11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;

4-Fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

5-Fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;

1-[11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-4-yl]-1-ethanone;

1-[11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-4-yl]-1-propanone;

6-Methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

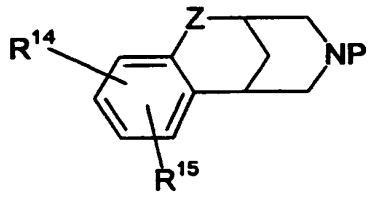
6-Methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6,7-Dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

5,7,14-Triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,11,18-Triazapentacyclo[14.3.1.$0^{2,14}$.$0^{4,12}$.$0^{6,11}$]icosa-2(14),3,5,12-tetraene;
7-Ethyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-Methyl-7-propyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Ethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Butyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Isobutyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Butyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Isobutyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,11,18-Triazapentacyclo[14.3.1.$0^{2,14}$.$0^{4,12}$.$0^{5,10}$]icosa-2(14),3,10,12-tetraene;
5,6-Dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Ethyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Ethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-Methyl-5-propyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Isobutyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Propyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Isobutyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-(Trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,8,15-Triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
7-Methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6-Methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6,7-Dimethyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
7-Oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-Methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-Ethyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-Propyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5-Methyl-7-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5-Oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-Methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-Ethyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-Propyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
7-Methyl-5-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
4,5-Difluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene4-chloro-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-Chloro-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
4-(1-Ethynyl)-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-(1-Ethynyl)-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and
4,5-Dichloro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene.

This invention also relates to compounds of the formula



(I)

wherein wherein Z is CH_2, C(=O) or CF_2; P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or (C_1-C_6)alkyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, $-C(=O)(C_1$-$C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected, independently, from hydrogen, hydroxy, nitro, amino, $-O(C_1$-$C_6)$alkyl or halo; with the proviso that R^{14} and R^{15} can not both be hydrogen when P is hydrogen or methyl. Such compounds are useful as intermediates in the synthesis of compounds of the formula I.

Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein, includes straight, branched or cyclic, and may include straight and cyclic alkyl moieties as well as branched and cyclic moieties.

The term "alkoxy", as used herein, means "alkyl-O-", wherein "alkyl" is defined as above.

The term "alkylene, as used herein, means an alkyl radical having two available bonding sites (i.e., -alkyl-), wherein "alkyl" is defined as above.

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The compounds of formula I may have optical centers and therefore may occur in different enantiomeric configurations. The invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula I, as well as racemic and other mixtures thereof.

The present invention also relates to all radiolabelled forms of the compounds of the formulae I. Preferred radiolabelled compounds of formula I are those wherein the radiolabels are selected from as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-

infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically accepable salt thereof, and a pharmaceutically acceptable carrier.

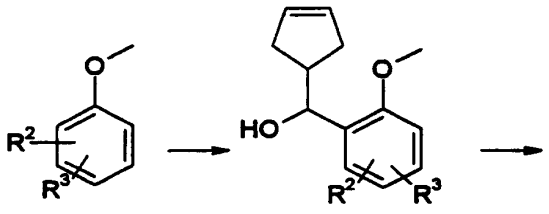
This invention also relates to the pharmaceutically acceptable acid addition salts of the compounds of formula I. Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I are the salts of hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, malate, di-p-toluoyl tartaric acid, and mandelic acid.

Detailed Description of the Invention

Except where otherwise stated, R^1 through R^{18}, m and P, and structural formula I in the reaction schemes and discussion that follow are defined as above.

5

SCHEME 1



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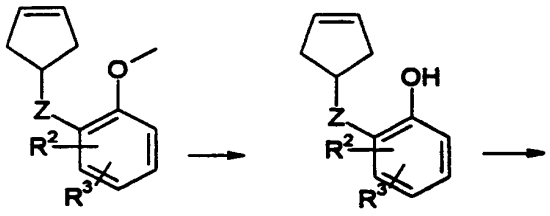
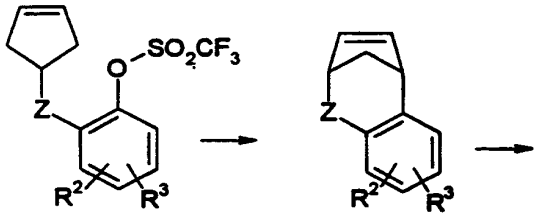
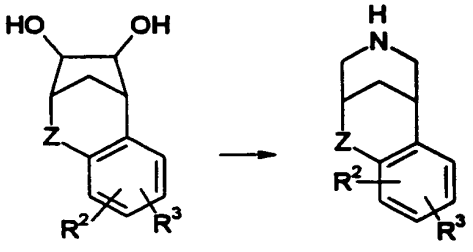


IV V



VI VII



VIII IA

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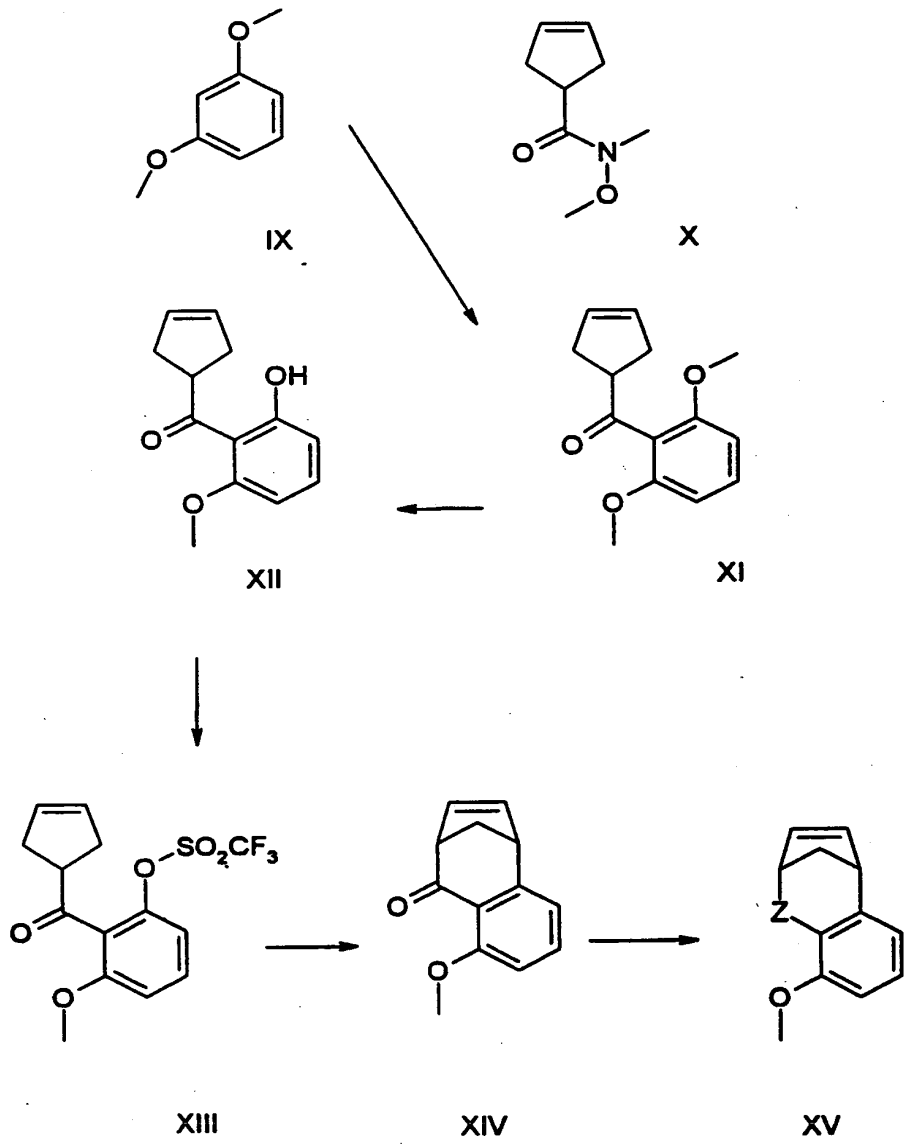
SCHEME 2



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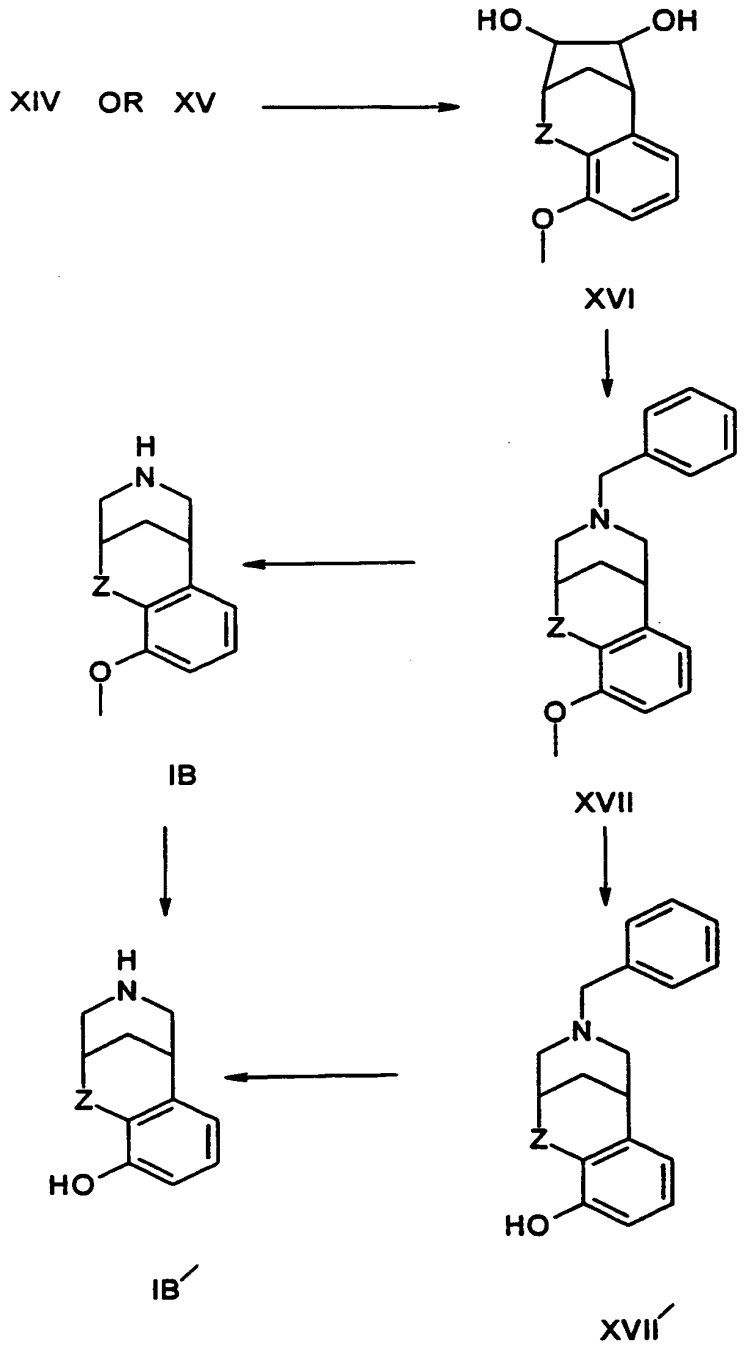
SCHEME 2 continued



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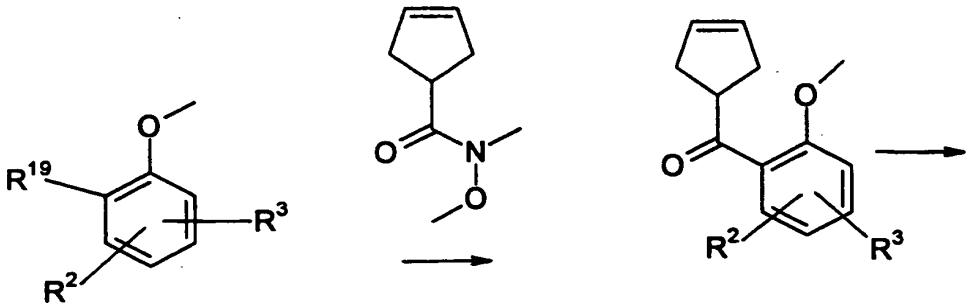
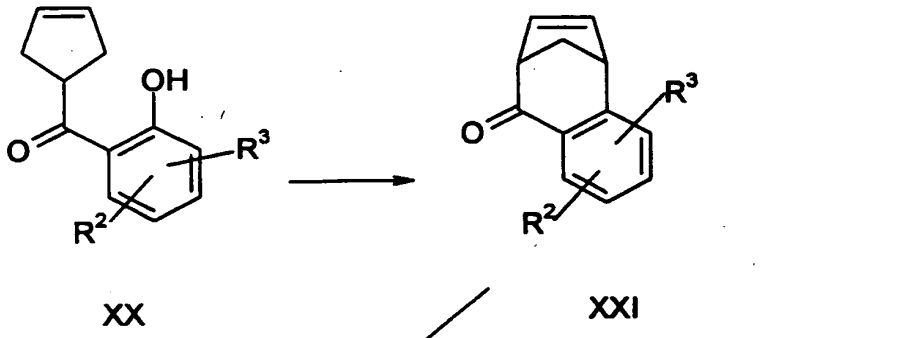


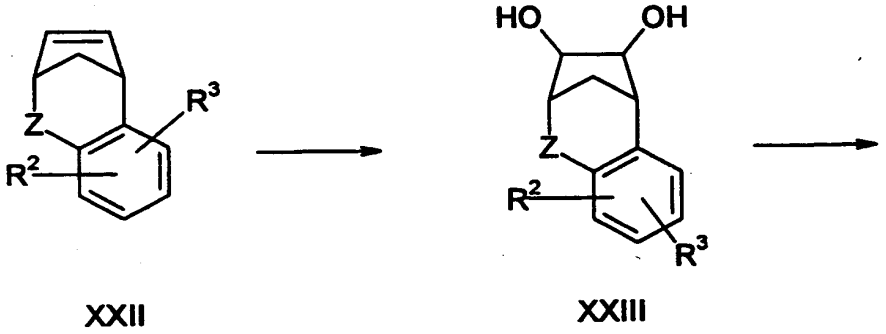
XVIII

XIX



XX

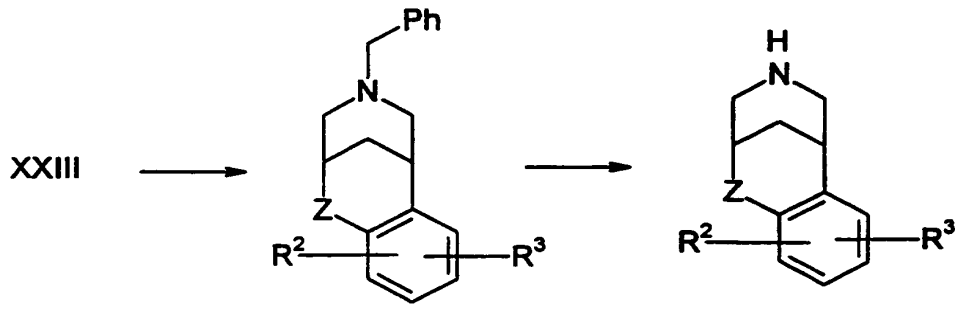
XXI



XXII

XXIII

SCHEME 3 continued

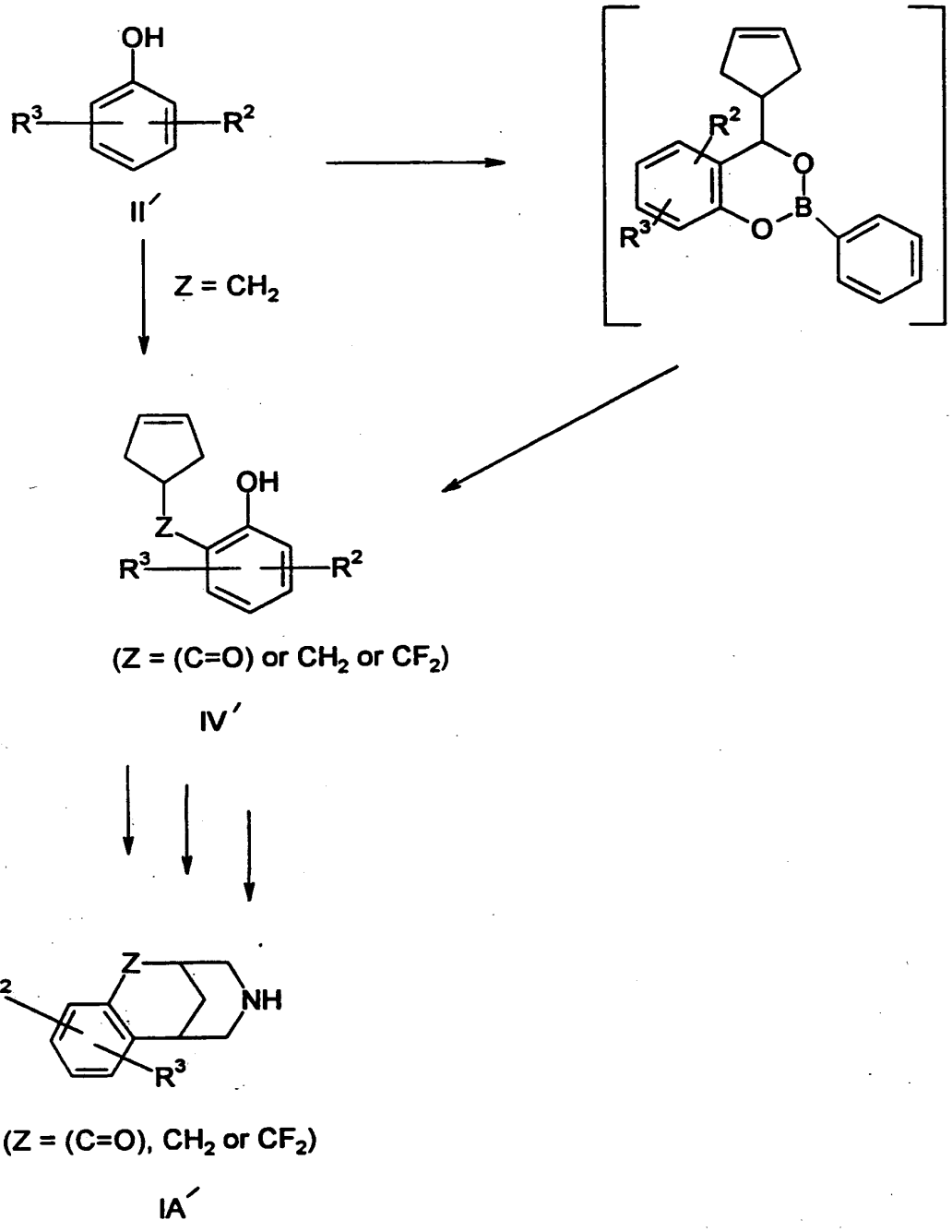


(Ph=phenyl)

XXIV

IC

SCHEME 4



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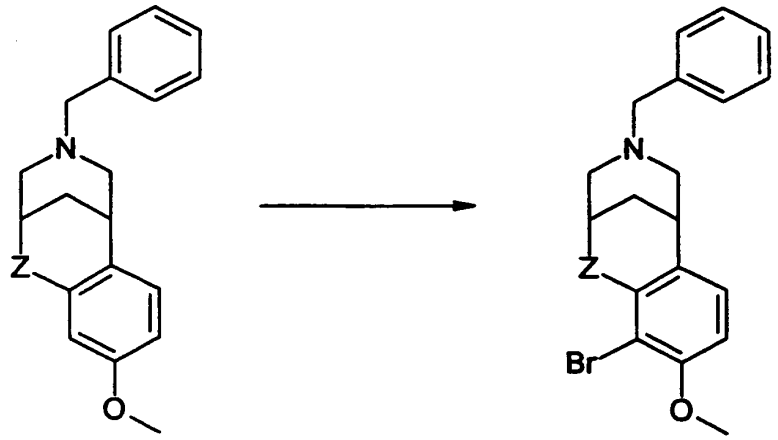
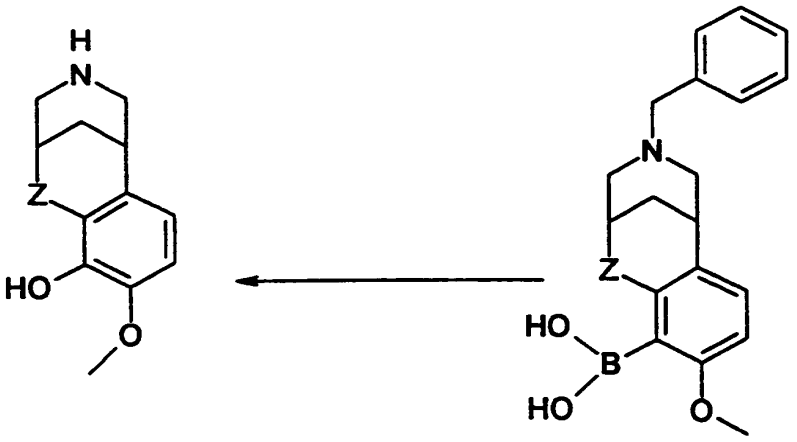
SCHEME 5



XXIV XXIVA



IC XXIVB

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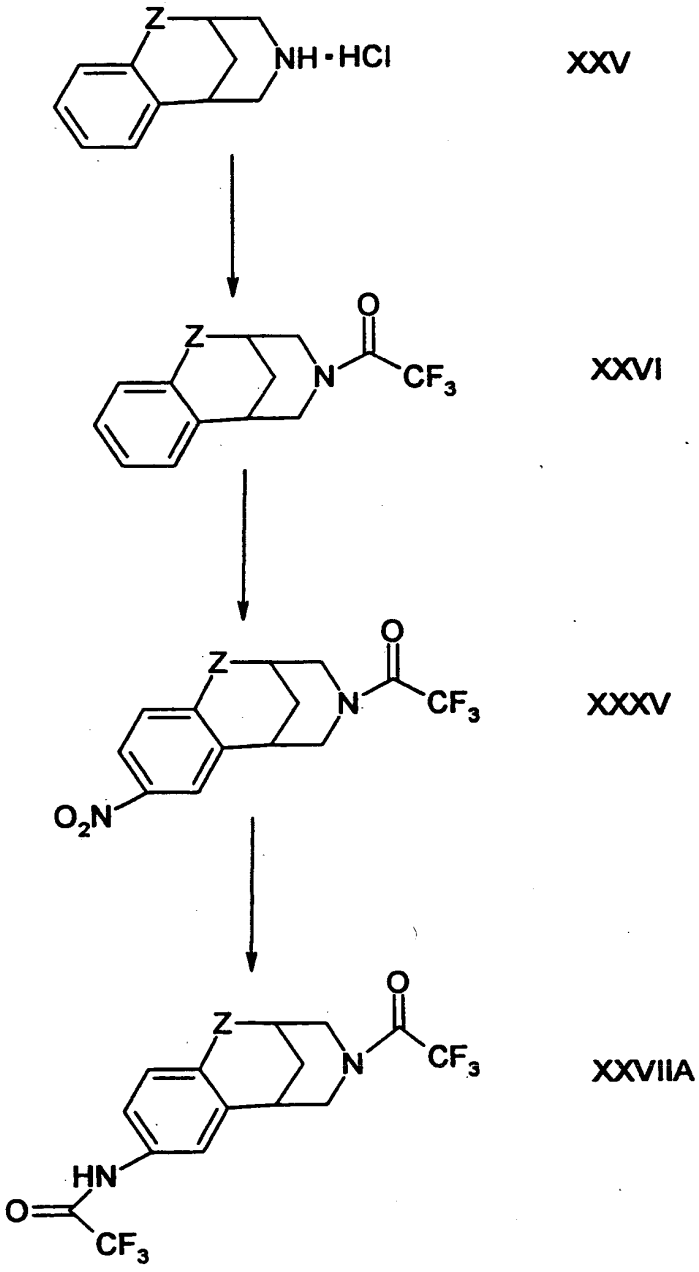

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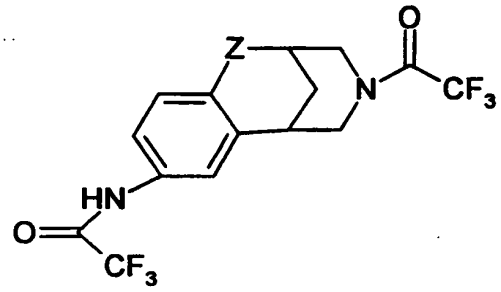

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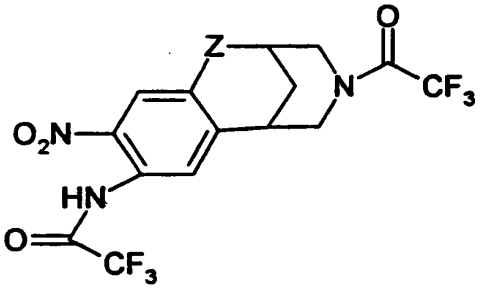

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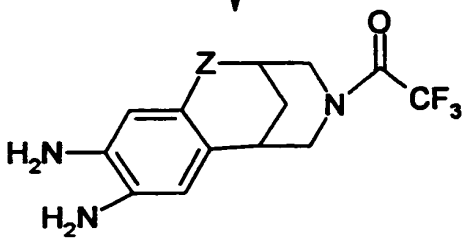

XXVIIB

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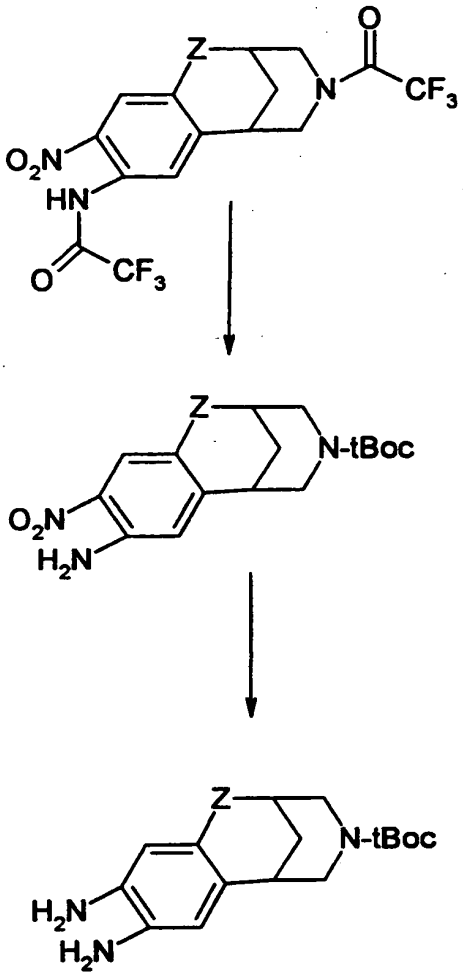

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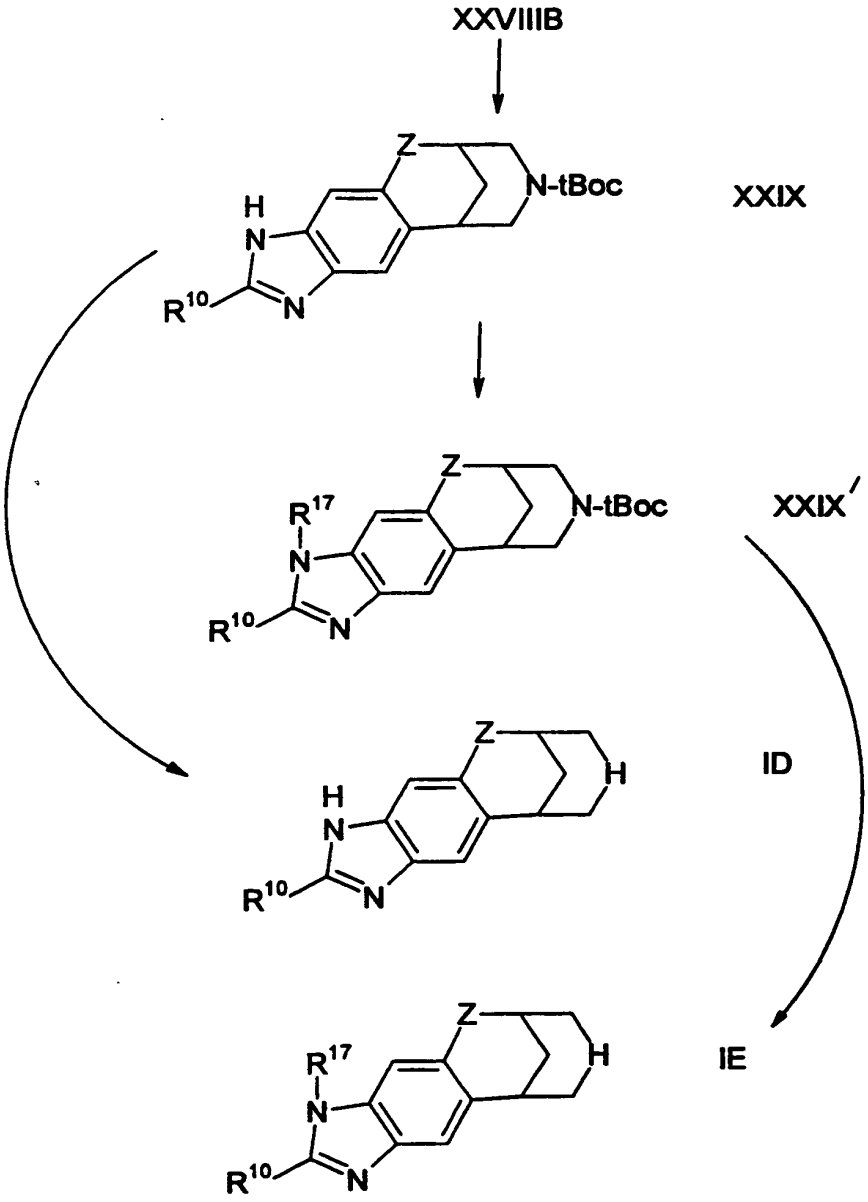

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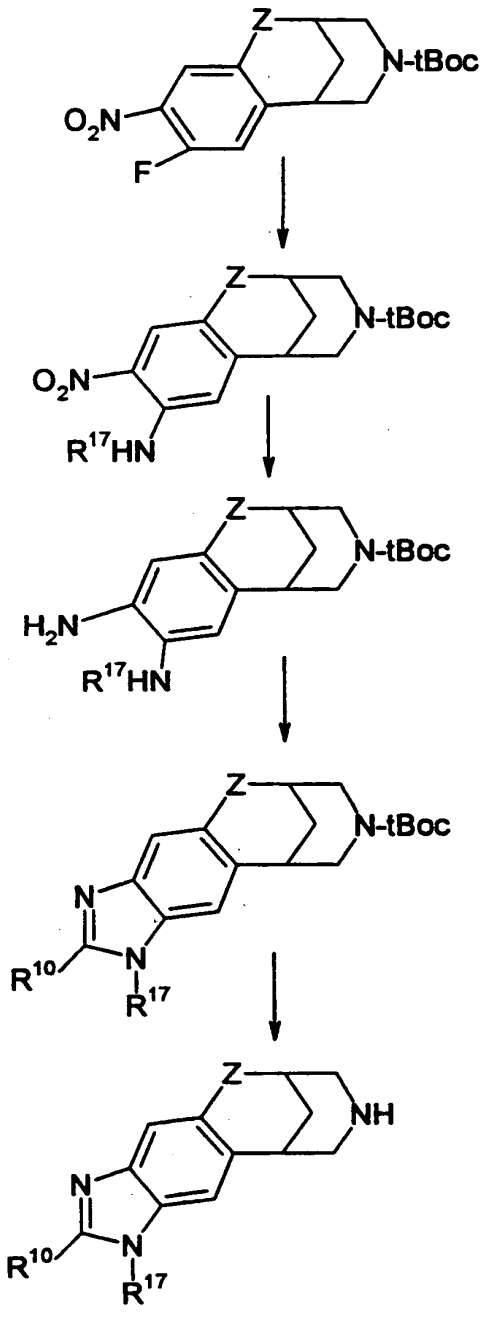

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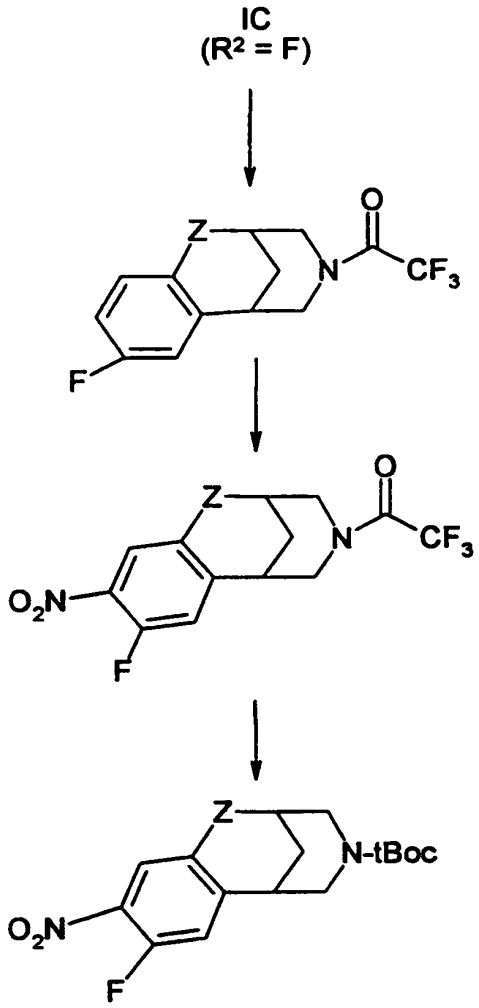

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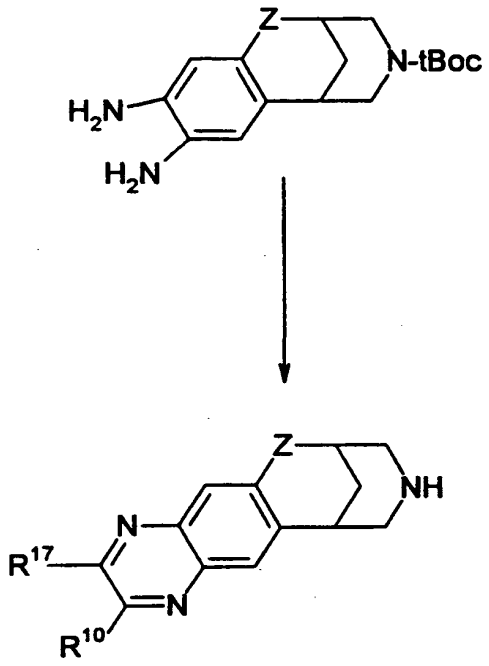

XXVIIIB

IF

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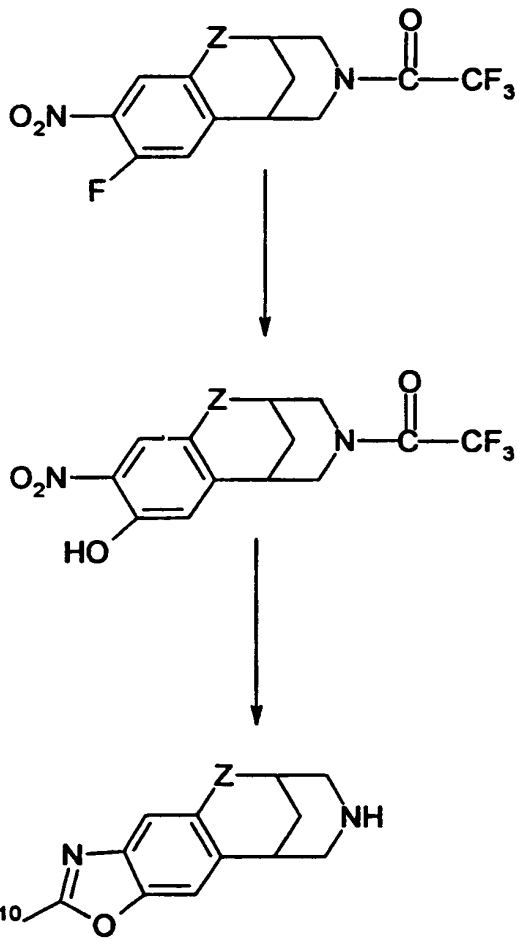
SCHEME 10



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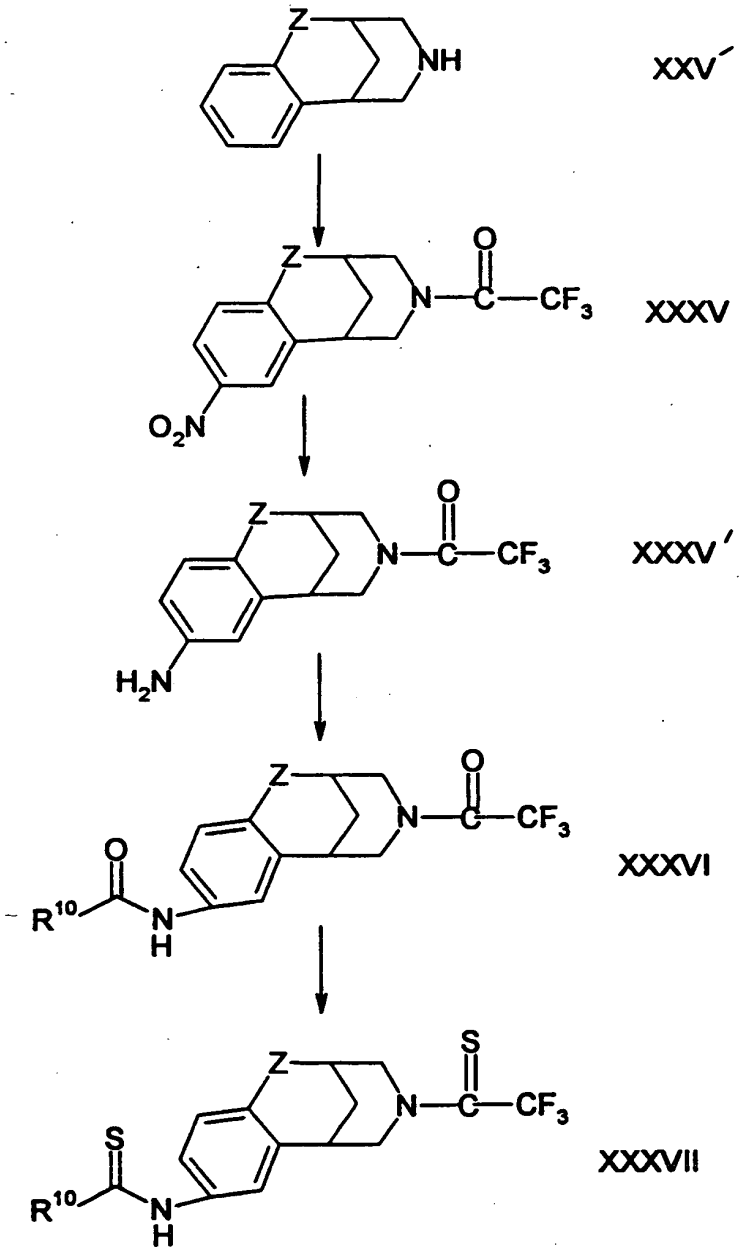

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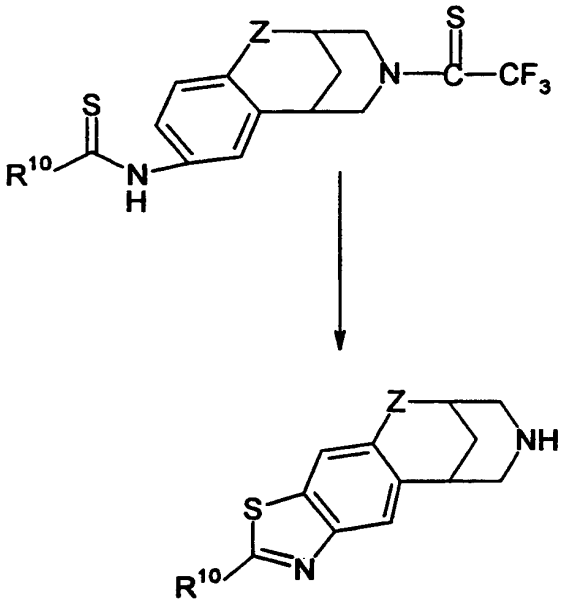
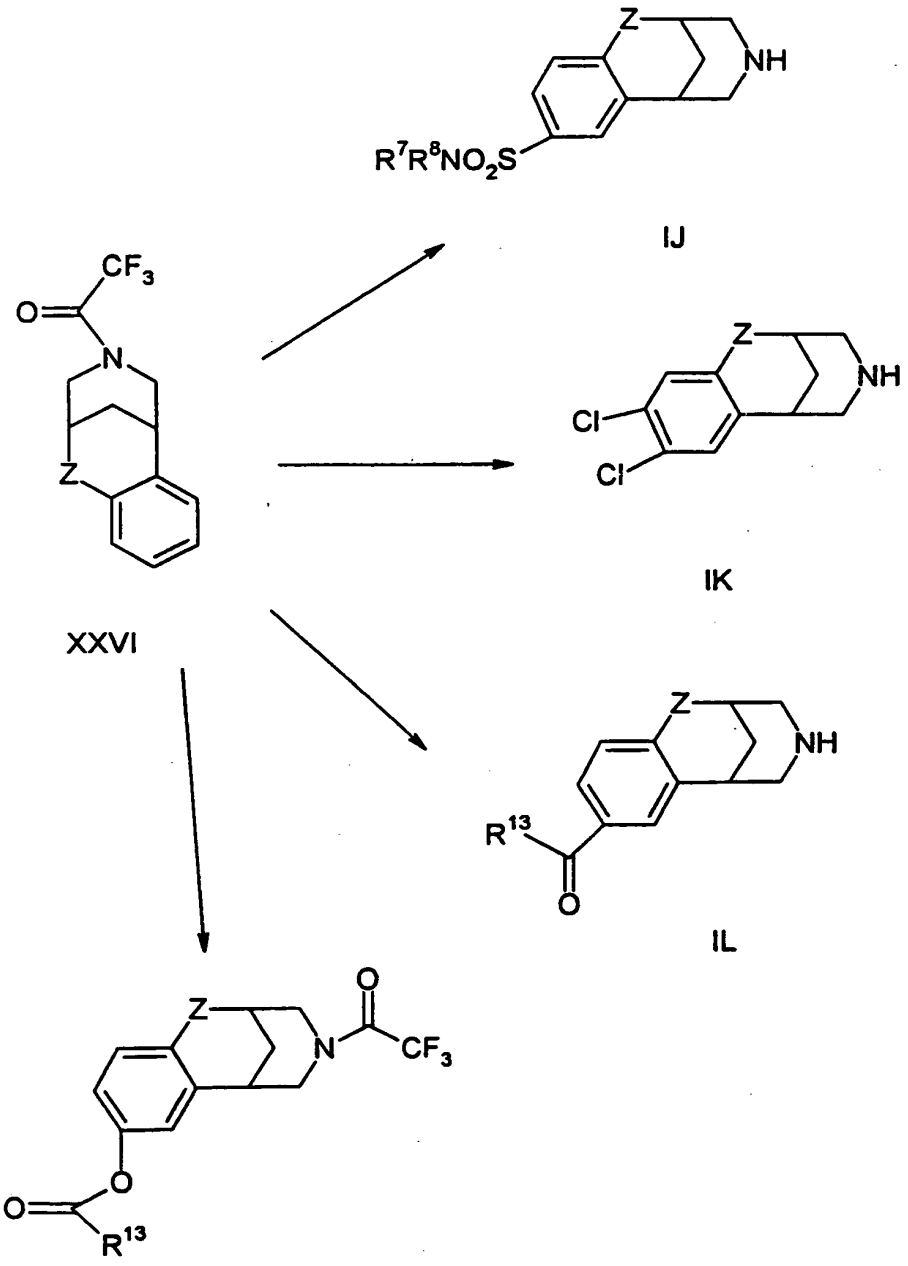


XXXVII

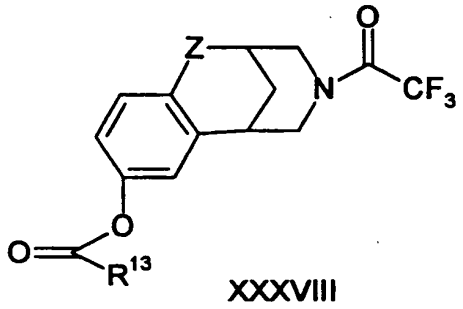
IH

SCHEME 12



XXXVIII

SCHEME 12 Continued



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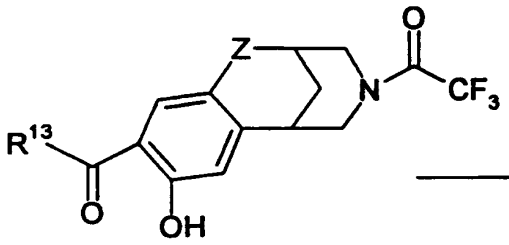

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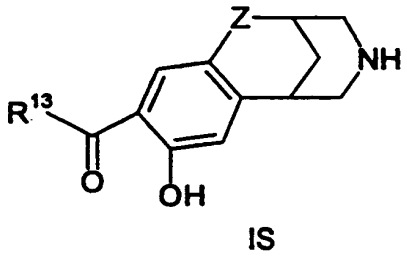

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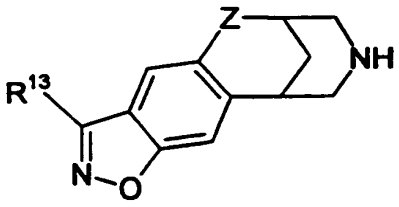
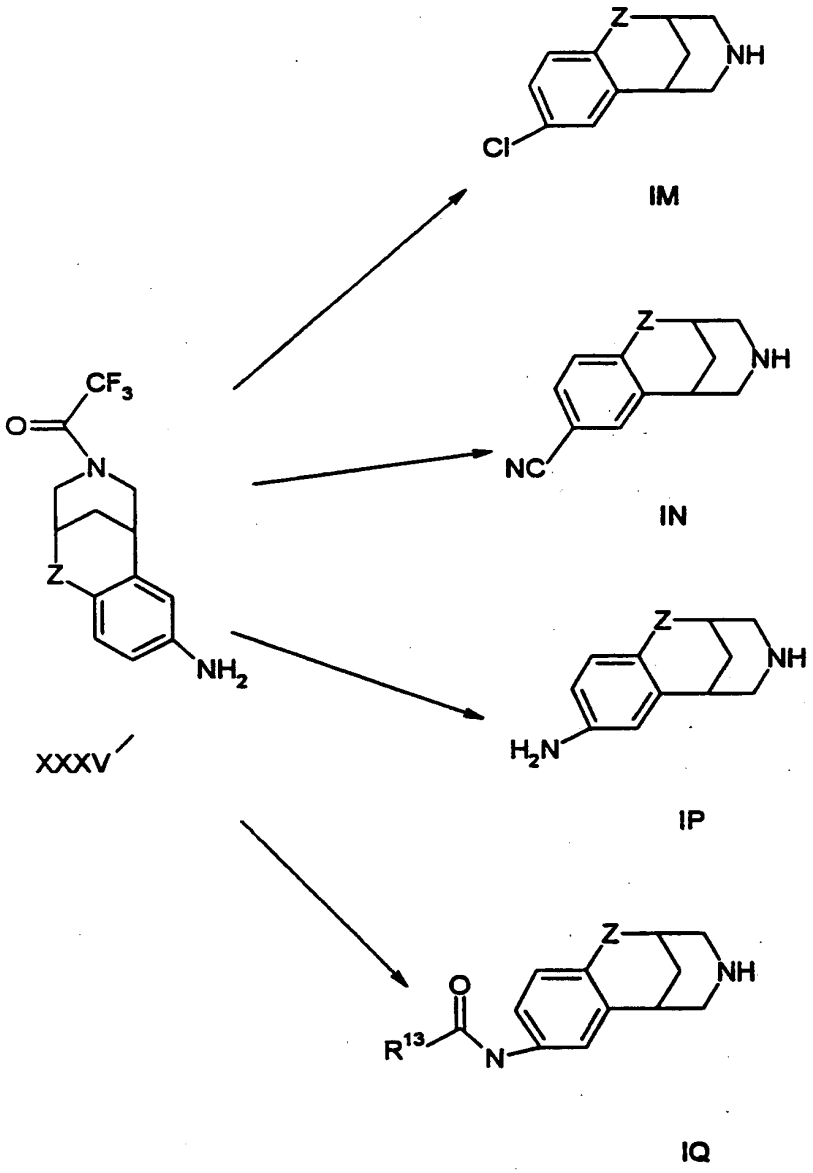


IT

SCHEME 13



Scheme 1-13 illustrate methods of synthesizing compounds of the formula I. Schemes 1-4 illustrate such methods wherein the substituent groups R^2 and R^3 are attached prior to cyclization to form the tricyclic nucleus of formula I, which is represented by the free base of structural formula IA (Scheme 1) or IC (Scheme 3) wherein R^2 and R^3 are hydrogen. Schemes 5-13 illustrate methods of forming compounds of the formula I from starting materials that contain such nucleus.

Referring to Scheme 1, the starting material of formula II is converted to a compound of formula III by the following process. The starting material of formula II is reacted with approximately 1 equivalent of a strong base such as n-butyllithium in a solvent such as anhydrous THF, ether or methyl t-butyl ether, at a temperature from about -78°C to about -65°C. This metalation occurs over a period of from about ten minutes to five hours, typically in about two hours with the temperature maintained below -65°C. The anion, so-produced, is then treated with cyclopent-3-ene carboxaldehyde in the same solvent at such a rate so as to maintain the temperature below -65°C. The reaction is then quenched by addition of the reaction mixture to an aqueous acidic medium and worked up.

The compound of formula III, so-produced, is then reduced at the benzylic position by the action of trifluoroacetic acid and a reducing agent such as triethylsilane, to form the corresponding compound having formula IV. This reaction is generally conducted in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane (DCE) or methylene chloride, at about room temperature, for a period of about 6 to 24 hours, preferably for about 18 hours.

This compound of formula IV is then converted into the corresponding compound of formula V by treating it with equivalent amounts of tetrabutyl ammonium iodide and boron trichloride in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane (DCE) or methylene chloride. This reaction is typically conducted at a temperature of -78°C initially, and then allowed to react over a period of about two hours while warming to ambient temperature.

The resulting compound of formula V is then reacted with trifluoromethanesulfonic anhydride in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane (DCE) or methylene chloride, in the presence of a base such as pyridine or 3-methylpyridine, to form the corresponding trifluoromethanesulfonic acid ester of formula VI. Typically, the initial reaction temperature is about -78°C and the reaction is allowed to warm to room temperature to complete the reaction.

The trifluoromethanesulfonic acid ester of formula VI is then reacted under Heck cyclization conditions to produce the corresponding compound of formula VII. This reaction may be performed with or without a solvent. Suitable solvents include N,N-

dimethylformamide (DMF), N-methylpyrrolidone (NMP) and toluene. Temperatures ranging from about 60°C to about 130°C are suitable, and the reaction is generally run for a period of about 1 to 48 hours. Preferably, the reaction is conducted at a temperature of about 100°C for about 2-18 hours. Catalysts in this reaction are generated *in situ* by treatment with sources of palladium, such as palladium acetate ($Pd(OAc)_2$), palladium dichloride ($PdCl_2$) or palladium in the reduced zero oxidation state such as palladium on carbon (Pd/C) or tris(dibenzylidene acetone)dipalladium(O) ($Pd_2(dba)_3$). Analogous nickel catalysts can also be used. The amount of catalyst required is about 0.1 mole % to a stoichiometric amount. Preferably, about 2-10 mole % of the palladium or nickel catalyst is used. Often, conditions used in these reactions include ligands such as triphenylphosphine or tri-o-tolylphosphine, or bidentate ligands such as DPPF, DPPE, DPPB, DPPP (DPP=bis-diphenylphosphine, F=ferrocene, E=ethyl, P=propane, B=butane) or any of a variety of chiral ligands such as BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) or arsenate ligands, or bidentate combinations of these ligands with chiral directing groups, such as, for example, oxazolines, though the inclusion of ligands may not be necessary in all cases. If ligands are used in combination with palladium or nickel sources, they are typically used in amounts from about 0.5 to about 4 molar equivalents of the palladium or nickel catalyst.

The above reaction is conducted in the presence of a base, typically a tertiary amine base such as triethylamine or diisopropylethylamine. Other bases such as carbonates or acetates, (e.g., potassium carbonate, sodium carbonate, sodium acetate or potassium acetate) may also provide adequate or desirable results. In some cases, as exemplified in the experimental examples, it is beneficial to use a tertiary amine base, as described above, in combination with catalytic acetate or carbonate salt such as potassium acetate, in an amount equivalent to the phosphine ligand to accelerate the reaction. An additional additive that may be useful is an alkyl ammonium halide salt, such as tetrabutyl ammonium chloride. These conditions are common, and are based on the conditions described by Jeffrey T. in J. Chem. Soc., Chem. Commun., 1984, 1287 and Synthesis, 1987, 70. These reactions are generally performed under an atmosphere of nitrogen or argon, but may or may not require the presence of oxygen.

Reaction of the compound of formula VII with osmium tetroxide and a reoxidant such as N-methylmorpholine-N-oxide (NMO) in acetone and water at about room temperature yields the corresponding compound of formula VIII.

The compound having formula VIII is then converted into the desired corresponding compound of formula IA using the following procedure. First, the compound of formula VIII is reacted with sodium periodate in a mixture of a chlorinated hydrocarbon, preferably dichloroethane (DCE), and water, or with lead tetraacetate in a chlorinated hydrocarbon

solvent, at a temperature from about 0°C to about room temperature, to generate a dialdehyde or glycal intermediate. The product of this reaction is then reacted, with benzylamine (or ammonia) and sodium triacetoxyborohydride. Removal of the N-benzyl group yields the desired compound of formula IA. Removal of the benzyl group can be accomplished using methods well known to those of skill in the art, for example, by first optionally reacting the free base with one equivalent of acid, e.g., hydrochloric acid (to form the corresponding acid addition salt), and then with hydrogen and palladium hydroxide in methanol at about room temperature.

Alternatively, the reductive amination may be carried out in situ as follows. Oxidative cleavage of the diol of formula VIII performed using sodium periodate in aqueous THF or alcohol to form the dialdehyde/glycal intermediate referred to above. Treatment of this intermediate with excess benzylamine (or ammonia), palladium hydroxide and hydrogen at a temperature from about room temperature to about 70°C generates the desired compound of formula IA.

If the above method used leaves a benzyl group on the compound, removal of the benzyl group will yield the desired compound of formula IA. Removal of the benzyl group can be accomplished using methods well known to those of skill in the art, for example, optionally reacting the free base with one equivalent of acid, e.g., hydrochloric acid (to form the corresponding acid addition salt), followed by hydrogen and palladium hydroxide in methanol at about room temperature.

In the reductive animation step described above and throughout this document, alternatives to benzyl amine, such as ammonia, hydroxylamine, alkoxy amines, methyl amine, allyl amine, and substituted benzyl amines (e.g., diphenylmethyl amine and 2- and 4-alkoxy substituted benzyl amines) can also be used. They can be used as free bases, or as their salts, preferably their acetate salts, and can be subsequently removed by methods described for each by T. W. Greene and G.M. Wuts, "Protective Groups in Organic Synthesis", 1991, John Wiley & Sons, New York, NY.

The procedure described above and illustrated in Scheme 1 is preferred for making compounds of the formula I wherein R^2 or R^3 is susceptible to reacting to form an aryne or in another type of side reaction.

The procedure described above produces compounds of the formula IA wherein Z is CH_2. Compounds of the formula IA wherein Z is (C=O) can be formed using the procedure illustrated in Scheme 1, as described above, with the exception that the compound of formula III is oxidized, rather than reduced, at the benzylic position, to form a compound of the formula IV wherein Z is (C=O). This can be accomplished using methods well known to those of skill in the art such as by treatment with Jones reagent (chromic acid solution) in

ether or acetone at a temperature from about 0°C to about room temperature . Compounds of the formula IA wherein Z is CF_2 can be prepared in a similar manner by converting the oxidized compound of formula IV wherein Z is (C=O) into the corresponding compound of formula IV wherein Z is CF_2, and then continuing with the reaction sequence of Scheme 1. This conversion can be accomplished using methods well known in the art, such as by treatment with Lawesson's reagent. The reaction with Lawesson's reagent is generally carried out in a reaction inert solvent such as benzene or toluene, preferably toluene, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature.

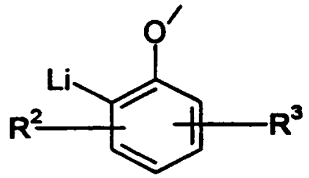
Scheme 2 illustrates an alternate method of preparing compounds of the formula I. This method is the preferred method for preparing such compounds wherein neither R^2 nor R^3 is susceptible to reacting in an undesireable side reaction. Referring to Scheme 2, the compound of formula IX is treated with a strong base such as n-butyllithium at a temperature from about room temperature to about the reflux temperature of the reaction mixture, in a solvent such as ether or t-butyl methyl ether. This metalation occurs over a period of from about 1 to 5 hours, typically in about 4 hours when the reaction is conducted at the reflux temperature in ether. The resulting anion is then cooled in the same solvent or in a solvent mixture such as one containing tetrahydrofuran (THF), to a temperature of about -78°C. This anion can then be reacted with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (X) at about -78°C, for about a half hour, with completion of the reaction occurring upon warming to ambient temperature. This reaction yields the compound of formula XI. The compound of formula XI is then dissolved in a solvent such as methylene chloride and treated with boron trichloride at about -78°C. After a period of 20 about minutes, the reaction is allowed to warm to about 0°C and is worked up. The resulting phenol of formula XII is then converted into the trifluoromethanesulfonic ester by the methods described above for generating the compound of formula XIII. The resulting ester can then be converted into a compound of formula XIV under Heck conditions, as described above.

Reduction of the compound of formula XIV using standard Wolff-Kishner conditions yields the compound of formula XV. These conditions are well known to those skilled in the art, and include reacting the compound of formula XIV with hydrazine and potassium hydroxide, first at a temperature of approximately 100°C in a solvent, usually ethylene glycol or diglyme, and then increasing the temperature to about 180-200°C. Reductions that are known in the art to be equivalent to the standard Wolff-Kishner reduction may also be used. The compound of formula XV can be converted into the compound of formula IB by a procedure analogous to the conversion of compounds of the formula VII into those of the formula IA in Scheme 1.

Rather than reducing the ketone in the compound of formula XIV, the corresponding compound wherein the oxo group is replaced by CF_2 can be formed by treatment with Lawesson's reagent, or using other methods for effecting this conversion that are well known to those of skill in the art.

Methyl ethers may be converted to their corresponding phenols by methods well known to those skilled in the art. This can be accomplished by exposing the compound of formula IB or XVII to hydrobromic acid and warming the resulting mixture to the reflux temperature for a period of about 1 hour. This reaction produces the corresponding phenol of formula IB' or XVII', respectively.

An alternative to the methods described in Schemes 1 and 2 for generating aryl anions is to use halogen-metal exchange conditions. For example, a compound of the formula XVIII, illustrated in Scheme 3, wherein R^{19} is bromo or iodo, can be treated with an alkyllithium base such as n-butyllithium, at a temperature form about -78°C to 20°C, typically at about -78°C to produce an aryl anion of the formula



XVIII'

The anion produced in this reaction can then be reacted with an aldehyde, such as described in Scheme 1, or an appropriate disubstituted amide, as described in Scheme 2, to produce a compound of the formula XIX. (Rather than reacting the compound of formula XVIII with an alkyllithium base, as described immediately above, such compound can optionally first be converted into a Grignard reagent (R^{19} → MgR^{19}) using standard methods, and then reacted as described above for compounds of the formula XVIII' to prepare a compound of the formula XIX).

The resulting compound of formula XIX can then be converted into a compound of the formula IC (Scheme 3) using the methods described above for the conversion of compounds of the formula XI into those of the formula IB (Scheme 2) and for the conversion of compounds of the formula IV into those of the formula IA (Scheme 1).

The generation of anions at the ortho position of the aromatic systems employed in the synthetic procedures described in this application is encompassed under a general

synthetic strategy known to those skilled in the art as Directed Ortho Metalation (DOM). Within this area, a number of functional groups known as Directed Metalation Groups (DMGs) have been studied for this purpose, and some are reviewed in Snieckus, V. *Chem Rev.* **1990**, 879. Where applicable, DMGs other than those utilized in this work may be equally applicable to the preparation of the compounds and intermediates described herein.

An alternative method for the generation of compounds similar to compounds of the formula V, XII or XX appears in Scheme 4. In this method, cyclopent-3-ene carboxaldehyde and a phenol are combined with an aryl boronic acid and an acid catalyst such as an acetic acid (optionally substituted with halo substitutents at the alpha position to modulate the acidity of the reaction), or with a aryl boron dihalide, which, by its nature, will generate a mineral acid under the conditions of the reaction, in a solvent such as benzene, toluene, dioxane or dichloromethane, preferably in benzene. The temperature of the reaction is typically the reflux temperaure, or at a temperature that allows any of the standard methods for removal of water generated in the reaction to be removed at a rate that allows the desired reaction to occur. A convenient method employs a Dean-Stark trap to remove water formed in the reaction. Typically, the reaction is conducted for a period of 3-48 hours, generally 10-24 hours, or until the theoretical amount of water has been collected. At this time the reaction is freed of solvent and then subjected to conditions as described above for reduction of benzylic hydroxyl groups or ethers, for example, treatment of this intermediate with trifluoroacetic acid and a reducing agent such as triethylsilane. This reaction is conducted in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane (DCE) or methylene chloride, at or about room temperature for a period of 6 to 24 hours, preferably 18 hours.

The above reaction produces a compound of the formula IV' wherein Z is CH_2. The corresponding compounds of the formula IV ' wherein Z is (C=O) and CF_2 can be formed using the methods described above for preparing compounds of the formula IV (Scheme 1) wherein Z is (C=O) or CF_2.

The resulting compounds of formula IV' (Z is (C = O), CH_2 or CF_2) are is then converted into the corresponding compound of formula IA' using the methods described above and depicted in Scheme 1 for the preparation of compounds of the formula IA.

Scheme 5 illustrates a method for the introduction of substituents, such as bromine and oxygen, into compounds of the invention. Treatment of a compound of formula XXIV with bromine, under standard conditions known to those of skill in the art, for example, in a chlorinated hydrocarbon solvent such as chloroform, dichoroethane (DCE) or methylene chloride, at a temperature of about 0°C to about room temperature, preferably at room temperature, in the presence of a base such as sodium acetate, generates the corresponding compound of formula XXIVA. The bromide so produced (XXIVA) can then be converted, by

the process of halogen-metal exchange described above, to a lithium anion derivative, which can then be treated with a variety of electrophiles, for example, trialkylborates, typically at temperatures ranging between -78 and 0°C to produce the corresponding boronic acid derivative of formula XXIVB.

This compound can then be converted to a variety of derivatives accessible through Suzuki coupling chemistry under standard conditions known to those of skill in the art. Alternatively these boronic acid compounds may be converted into the corresponding phenol derivatives, by reaction with hydrogen peroxide or N-methylmorpholine, in a solvent such as THF, or by any other standard methods known to those of skill in the art. Removal of the benzyl protecting group by methods described above yields the desired compound of formula IC'.

Phenols prepared as described above and in the experimental section can be converted to the corresponding trifluoromethanesulfonic esters. These derivatives, as well as the bromides formula XXIVA, can be used to access a variety of other substituents (i.e., other values of R^2 and R^3) such as aryl, acetylene and vinyl substituents, as well as the corresponding carbonyl esters and amides, by palladium and nickel catalyzed processes known to those of skill in the art, such as Heck, Suzuki and Stille couplings and Heck carbonylations. Additionally, phenols can be alkylated by a variety of common methods to prepare ethers. Additionally, esters may be treated with nucleophiles, such as Grignard reagents to prepare the corresponding tertiary alcohols. Examples of these transformations appear in the Experimental Examples.

Scheme 6 illustrates the preparation of certain intermediates used in the procedure of Scheme 7. Referring to Scheme 6, the starting material of formula XXV is reacted with trifluoroacetic anhydride, in the presence of pyridine, to form the compound of formula XXVI. This reaction is typically conducted in methylene chloride at a temperature from about 0°C to about room temperature.

The compound of formula XXVI, when Z is not (C=O), can then be converted into the nitro derivative of formula XXXV by the following process. The compound of the formula XXVI is added to a mixture of 2 or more equivalents of trifluoromethanesulfonic acid (CF_3SO_2OH) and 1 to 1.5 equivalents of nitric acid, in a chlorinated hydrocarbon solvent such as chloroform, dichoroethane (DCE) or methylene chloride. The resulting mixture is allowed to react for about 5 to 24 hours. Both of the foregoing reactions are generally conducted at a temperature ranging from about -78°C to about 0°C for about 2 hours, and then allowed to warm to room temperature for the remaining time.

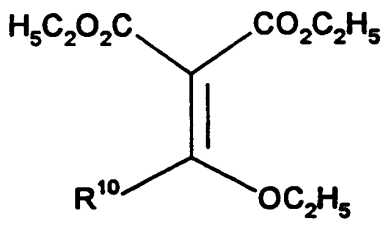
Compounds of the formula XXXV wherein Z is (C=O) can be prepared by oxidizing the analogous compounds wherein Z is CH_2 as described by Kapur et al., Can. J. Chem., 66, 1988, 2888-2893.

Reduction of the compound of formula XXXV, using methods well known to those of skill in the art, yields the corresponding aniline. This reduction can be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide, and running the reaction in methanol or ethanol at about room temperature. The intermediate aniline is then converted into the trifluoroacetamide of formula XXVIIA as described above for the preparation of compounds of the formula XXVI.

Mononitration of the compound of formula XXVIIA, as described above for the preparation of compounds of the formula XXXV, yields the corresponding nitro derivative of formula XXVIIA'. Treatment of the nitro derivative of formula XXVIIA' with aqueous bicarbonate in methanol or THF, at a temperature from about 20°C to about 70°C, followed by reduction of the nitro group as described above, yields the corresponding compound of formula XXVIIB.

Referring to Scheme 7, the compound of formula XXVIIA' is converted into the corresponding compound wherein the trifluoroacetyl protecting group is replaced by a t-Boc protecting group (XXVIIIA) by reacting it first with an alkali metal or alkaline earth metal (or ammonium) hydroxide or carbonate, and then reacting the isolated product from the foregoing reaction with di-t-butyldicarbonate. The reaction with the alkali or alkaline earth metal (or ammonium) hydroxide or carbonate is generally carried out in an aqueous alcohol, dioxane or tetrahydrofuran (THF) at a temperature from about room temperature to about 70°C, preferably at about 70°C, for about one to about 24 hours. The reaction of the isolated, unprotected amine or an acid addition salt of such amine, from the above reaction with di-t-butyldicarbonate is preferably carried out in a solvent such as THF, dioxane or methylene chloride at a temperature from about 0°C to about room temperature. This reaction may or may not be conducted in the presence of a base. When the reactant is a salt of the amine, use of a base is preferred. The resulting compound of formula XXVIIIA can be converted into the corresponding diamino derivative of formula XXVIIIB using the procedure described above for converting compounds of the formula XXVIIA' into the corresponding diamino compounds of formula XXVIIB.

The conversion of the compound of formula XXVIIIB into the desired compound of the formula XXIX can be accomplished by reacting the compound of formula XXVIIIB with a compound of the formula



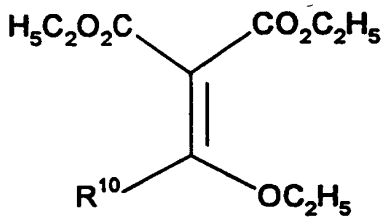
wherein R^{10} is hydrogen, (C_1-C_6) alkyl optionally substituted with from one to seven fluorine atoms, aryl-(C_0-C_3) alkyl wherein said aryl is selected from phenyl and naphthyl, or heteroaryl-(C_0-C_3) alkyl wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteratoms selected from oxygen, nitrogen and sulfur, and wherein each of the foregoing aryl and heteroryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from (C_1-C_6) alkyl optionally substituted with from one to seven fluorine atoms, (C_1-C_6) alkoxy optionally substituted with from one to seven fluorine atoms and cyano. The preferred solvent for this reaction is a 10:1 mixture of ethanol:acetic acid. The reaction temperature can range from about 40°C to about 100°C. It is preferably about 60°C. Other appropriate solvents include acetic acid, ethanol and isopropanol.

Alternate methods of preparing compounds of the formula XXIX from the compound of formula XXVIIIB are described by Segelstein et al., Tetrahedron Lett., 1993, 34, 1897.

Removal of the t-Boc protecting group from the compound of formula XXIX yields the corresponding compound of formula ID. The protecting group can be removed using methods well known to those of skill in the art. For example, the compound of formula XXIX can be treated with an anhydrous acid such as hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, preferably hydrochloric acid in ethyl acetate, at a temperature from about 0°C to about 100°C, preferably from about room temperature to about 70°C, for about one to 24 hours.

The compound of formula XXIX can be converted into the corresponding compound of formula IE by reacting it with a compound of the formula $R^{17}Z$, wherein R^{17} is defined as R^{10} is defined above, and Z is a leaving group such as a halo or sulfonate (e.g., chloro, bromo, iodo, mesylate or tosylate), in the presence of a base such as an alkali metal hydride, hydroxide or carbonate, preferably potassium hydroxide, in a polar solvent such as water, dimethylsulfoxide (DMSO), THF or DMF, preferably a mixture of DMSO and water, and then removing the protecting group as described above. The reaction with $R^{17}Z$ is generally carried out at a temperature from about room temperature to about 100°C, preferably at about 50°C, for about five hours. Subsequent removal of the protecting group, as described above, yields the desired compound of formula IE.

Scheme 8 illustrates an alternative method of preparing compounds of the formula IE from the compound of formula XXVIIIA'. This method is the preferred method of making compounds of the formula IE wherein R^{17} is a group such as an aryl or heteroaryl containing group, or when R^{17} can not be attached, as illustrated in Scheme 7, by alkylation or aryl substitution methods. Referring to Scheme 8, the compound of formula XXVIIIA' is reacted with the appropriate compound of formula $R^{17}NH_2$ in a polar solvent such as THF, DMF or DMSO, preferably THF, at a temperature from about room temperature to about 100°C, preferably at the reflux temperature, for about four to eighteen hours. This reaction produces a compound of the formula XXX. The resulting compound of formula XXX is then converted into the corresponding compound of the formula XXXI by reducing the nitro group to an amino group using methods well known to those of skill in the art. Such methods are referred to above for the conversion of the compounds of the formula XXVIIA' into a compound of the formula XXVIIB in Scheme 6. Closure of the imidazole ring to form the corresponding compound of formula XXXII can then be accomplished by reacting the compound of formula XXXI from the above reaction with a compound of the formula

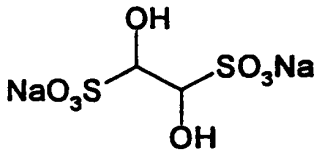


(wherein R^{10} is defined as above) as described above for converting compounds of the formula XXVIIIB into those of the formula XXIX.

Removal of the protecting group from the compound of formula XXXII yields the corresponding compound of formula IE. This can be accomplished using methods well known in the art, for example, as described above for forming compounds of the formula ID from the corresponding compounds of the formula XXIX.

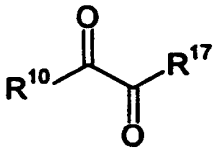
Compounds of the formula XXVIIIA', which are the starting materials used in the process of Scheme 8, can be synthesized as depicted in Scheme 8A and described below. The appropriate compound of formula IC (Scheme 3) wherein R^2 is fluoro is converted into its trifluoroacetamide derivative of the formula ICTFA, using methods described above. Such derivative is then nitrated, as described above or using other methods well known to those of skill in the art, to provide the corresponding nitro derivative of formula ICTFA'. Subsequent removal of the trifluoroacetamide group with an alkali metal carbonate or bicarbonate in methanol or THF, followed by protection with di-t-butyldicarbonate, as described above, yields the corresponding compound of formula XXVIIIA'.

Scheme 9 illustrates a method of preparing compounds of the formula IF, wherein R^{10} and R^{17} are as defined above. Referring to Scheme 9, the compound of formula XXVIIIB is reacted with a compound of the formula



(sodium bisulfite ethane dione addition adduct) in water or another polar solvent such as THF, DMF or DMSO, preferably a mixture of water and a water miscible solvent such as THF, for about one to four hours. The reaction temperature can range from about 40°C to about 100°C, and is preferably at about the reflux temperature.

Alternatively, the compound of formula XXVIIIB can be reacted with a compound of the formula



(double condensation reaction) in a polar solvent such as THF, water, or acetic acid, preferably a mixture of water and THF. This reaction is typically carried out at a temperature from about 40°C to about 100°C, preferably at the reflux temperature, for about two to four hours.

Both of the foregoing procedures can also be used to convert the corresponding compounds wherein the t-Boc protecting group is replaced by another protecting group such as TFA (e.g., compounds of the formula XXVIIB) into quinoxolines.

The desired quinoxoline of formula IF can then be formed by deprotecting the compound formed in either of the foregoing reactions, using the method described above for converting a compound of the formula XXIX into one of the formula ID or the method described above for removing the TFA group from a compound of the formula XXVIIA'.

Scheme 10 illustrates a method of preparing compounds of the formula I wherein R^2 and R^3, together with the benzo ring to which they are attached, form a benzoxazole ring system. Such a compound, wherein R^1 is hydrogen, is depicted in Scheme 10 as chemical formula IG. Referring to Scheme 10, a compound of the formula ICTFA', wherein Y is nitro or fluoro, is reacted with potassium acetate or another alkali or alkaline earth metal carboxylate in a solvent such as dimethylsulfoxide (DMSO), DMF or acetonitrile, preferably DMSO. This reaction is generally allowed to run for about 12-24 hours. Appropriate reaction temperatures range from about 70°C to about 140°C. Approximately 100°C is preferred.

The above reaction yields the compound of formula XXXIV, which can then be converted into the desired compound having formula IG by the following procedure. First, the compound of formula XXXIV is reduced by reaction with hydrogen and a palladium or platinum catalyst such as palladium hydroxide in methanol at a temperature from about 0°C to about 70°C, preferably at about room temperature, to form the corresponding amino derivative. The product of this reaction is then reacted with an acid chloride of the formula $R^{10}COCl$ or an acid anhydride of the formula $(R^{10}CO)_2O$ wherein R^{10} is $(C_1\text{-}C_6)$alkyl, or a compound of the formula $R^{10}C(OC_2H_5)_3$, in an appropriate inert solvent such as decalin, chlorobenzene or xylenes. A mixture of xylenes is preferred. This reaction is typically conducted at a temperature from about 120-150°C, preferably at about 140°C. When $R^{10}COCl$ is used as a reactant, it is preferable to add a stoicheometric amount of triethylamine (TEA) or another organic tertiary amine base and a catalytic amount of pyridinium p-toluenesulfonic acid or pyridinum p-toluenesulfonate (PPTS) to the reaction mixture. When $R^{10}C(OC_2H_5)_3$ is used as a reactant, it is preferable to add a catalytic amount of PPTS to the reaction mixture.

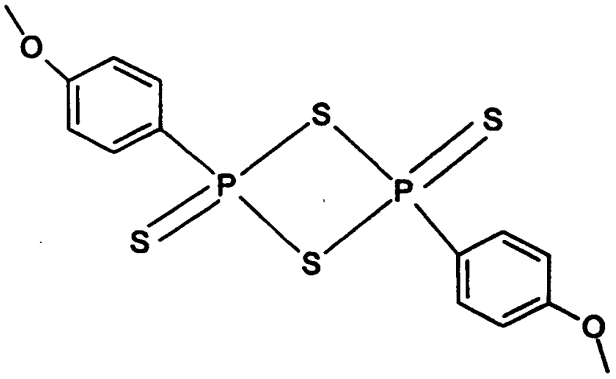
Removal of the trifluoroacetyl nitrogen protecting group yields the desired compound of the formula IG. This can be accomplished using methods well known to those of skill in the art, for example, reacting the protected compound with a lower alkanol and an aqueous alkali or alkaline earth metal (or ammonium) hydroxide or carbonate, aqueous sodium carbonate, at a temperature from about 50°C to about 100°C, preferably at about 70°C, for about two to six hours.

Scheme 11 illustrates the preparation of compounds of the formula I wherein R^1 is hydrogen and R^2 and R^3, together with the benzo ring to which they are attached, form a benzothiazole ring system. These compounds are referred to in Scheme 11 and hereinafter as "compounds of the formula IH". Referring to Scheme 11, the compound of formula XXV' is reacted with trifluoroacetic anhydride to form the corresponding compound wherein the ring nitrogen is protected by a trifluoroacetyl group, and the resulting nitrogen protected compound is then reacted with two equivalents of trifluoromethanesulfonic acid and one equivalent of nitric acid to form the corresponding compound of formula XXXV, wherein there is a single nitro substituent on the benzo ring. The reaction with trifluoroacetic acid is typically conducted in the presence of pyridine. Both of the above reactions are typically conducted in a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, at a temperature from about 0°C to about room temperature, preferably at about room temperature.

The above transformation can also be accomplished using other nitration methods known to those skill in the art.

Reduction of the nitro group to an amine group can be accomplished as described above to provide a compound of the formula XXXV'.

The compound of formula XXXV' is then reacted with a carboxylic acid halide or anhydride of the formula $R^{10}COX$ or $(R^{10}CO)_2O$, wherein X is halo, and pyridine, TEA or another tertiary amine base, to form a compound of the formula XXXVI, which can then be converted to the desired compound having formula XXXVII by reacting it with Lawesson's reagent, which is depicted below.



The reaction with $R^{10}COX$, wherein X is halo, or $(R^{10}CO)_2O$ is generally carried out at a temperature from about 0°C to about room temperature, preferably at about room temperature. The reaction with Lawesson's reagent is generally carried out in a reaction inert solvent such as benzene or toluene, preferably toluene, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature.

Closure to the benzothiazole ring and nitrogen deprotection to form the desired compound of formula IH can be accomplished by reacting the compound of formula XXXVII with potassium ferricyanide and sodium hydroxide in a mixture of water and methanol ($NaOH/H_2O/CH_3OH$), at a temperature from about 50°C to about 70°C, preferably at about 60°C for about 1.5 hours.

Schemes 12 and 13 illustrate methods of preparing compounds of the formula I wherein R^1 is hydrogen, and R^2 and R^3 represent a variety of different substituents, as defined above, but do not form a ring.

Scheme 12 illustrates methods of preparing compounds of the formula I wherein: (a) R^1 is hydrogen and R^2 is $R^7R^8NO_2S$-; (b) R^1 and R^2 are both chloro; and (c) R^1 is hydrogen and R^2 is $R^{13}C(=O)$-. These compounds are referred to in Scheme 12, respectively, as compounds of formulas IJ, IK and IL.

Referring to Scheme 12, compounds of the formula IJ can be prepared by reacting the compound of formula XXVI with two or more equivalents of a halosulfonic acid, preferably chlorosulfonic acid, at a temperature from about 0°C to about room temperature.

Reaction of the chlorosulfonic acid derivative so formed with an amine having the formula R^7R^8NH, wherein R^7 and R^8 are defined as above, followed by removal of the nitrogen protecting group, yields the desired compound having formula IJ.

Compounds of the formula IK can be prepared by reacting the compound of formula XXVI with iodine trichloride in a chlorinated hydrocarbon solvent, followed by removal of the nitrogen protecting group. The reaction with iodine trichloride is typically carried out at a temperature from about 0°C to about room temperature, and is preferably carried out at about room temperature. In a similar fashion, the analogous mono- or dibrominated or mono- or diiododinated compounds can be prepared by reacting the compound of XXVI with N-iodosuccinimide or N-bromosuccinimide in a trifluromethanesulfonic acid solvent, followed by removal of the nitrogen protecting group as described above.

Reaction of the compound of XXVI with an acid halide of the formula $R^{13}COCl$ or an acid anhydride of the formula $(R^{13}CO)_2O$, with or without a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, in the presence of Lewis acid such as aluminum chloride, at a temperature from about 0°C to about 100°C, followed by nitrogen deprotection, yields the compound of formula IL. The reaction with the acid halide or anhydride can be carried out using other known Lewis acids or other Friedel-Crafts acylations methods that are known in the art.

The reactions described herein in which NO_2, $-SO_2NR^7R^8$, $-COR^{13}$, I, Br or Cl are introduced on the compound of formula XXVI, as depicted in Scheme 12 and described above, can be performed on any analogous compound wherein R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$alkoxy or $-NHCONR^7R^8$, producing compounds of the formula I wherein R^2 and R^3 are defined as in the definition of compounds of the formula I above.

Compounds that are identical to those of the formula IL, but which retain the nitrogen protecting group, can be converted into the corresponding O-acyl substituted compounds, i.e., those wherein the $-C(=O)R^{13}$ group of formula IL is replaced with a $-O-C(=O)R^{13}$ group, using Baeyer-Villiger processes well known to those skilled in the art. The resulting compounds can be partially hydrolyzed to yield the corresponding hydroxy substituted compounds, and then alkylated to form the corresponding alkoxy substituted compounds. Also, such O-acyl substituted compounds can be used to prepare variably substituted benzisoxazoles, using methods well known to those of skill in the art such as using, in sequence, a Fries rearrangement, oxime formation, acylation and treatment with base. Such a process involves performing a Fries rearrangement of a compound of the formula XXXIII by treatment with a Lewis acid such as aluminum chloride ($AlCl_3$) neat or in a solvent such as chlorobenzene, at a temperature from about 100°C to about 200°C, preferably at about 170°C for about 1 to 2 hours, preferably for about 2 hours, to produce a compound of the

formula XXXIX. Cleavage of the protecting group provides the corresponding compound of formula IS. Alternatively, the compound of formula XXXIX can be converted into its oxime using standard methods well known to those skilled in the art, such as treatment with hydroxylamine hydrochloride in an alcohol (e.g., methanol), in the presence of a base such as sodium acetate, at a temperature from about 20°C to about 70°C, preferably at about 50°C for about 5 to 20 hours. Acylation of the oxime using methods well known in the art, such as treatment with acetic anhydride and pyridine, followed by treatment of the isolated acyl oxime with a base such as sodium hydride, in a solvent such as DMF, NMP or DMSO, produces the corresponding protected benzisoxazole. Cleavage of the protecting group under standard conditions, as described above, yields the desired compound of formula IT.

Scheme 13 illustrates methods of making compounds of the formula I wherein: (a) R^1 is hydrogen and R^2 is chloro; (b) R^1 is hydrogen and R^2 is cyano; (c) R^1 is hydrogen and R^2 is amino; and (d) R^1 is hydrogen and R^2 is $R^{13}C(=O)N(H)$-. These compounds are referred to in Scheme 13, respectively, as compounds of the formula IM, IN, IP and IQ.

Compounds of formula IM can be prepared from compounds of the formula XXXV' by generation of a diazonium salt with, for instance, an alkali metal nitrite and strong mineral acid (e.g., hydrochloric acid, sulfuric acid, hydrobromic acid) in water, followed by reaction with a copper halide salt, such as copper (I) chloride. Nitrogen deprotection by the methods described above yields the desired compound of formula IM. Alternative methods for the generation of diazonium salts, as known and practiced by those of skill in the art, can also be used. The foregoing reaction is generally carried out at temperatures ranging from about 0°C to about 60°C, preferably about 60°C for about 15 minutes to one hour.

Reaction of the diazodium salt, prepared as described above, with potassium iodide in an aqueous medium provides the analogous iodide derivative. This reaction is generally carried out at a temperature from about 0°C to about room temperature, preferably at about room temperature. The resulting compound, or its analogous N-tert-butylcarbonate protected form, can be used to prepare the corresponding cyano derivative by reaction with copper (I) cyanide and sodium cyanide in DMF, N-methylpyrrolidone (NMP), N,N-dimethylpropylurea (DMPU) or DMSO, preferably NMP, at a temperature from about 50°C to about 180°C, preferably at about 175°C. Nitrogen deprotection as described above provides the corresponding desired compound of formula IN.

The above described iodide, bromide or diazonium salt derivative can also be used to access a variety of other substituents such as aryl, acetylene and vinyl substituents, as well as the corresponding carbonyl esters and amides, by palladium and nickel catalyzed processes known to those of skill in the art, such as Heck, Suzuki and Stille couplings and Heck carbonylations.

Nitrogen deprotection of the compound of formula XXXV' provides the compound of the formula IP.

The compound of formula XXXV' can be reacted with a acyl group having the formula $R^{13}COCl$ or $(R^{13}CO)_2O$ using the methods described above, followed by nitrogen deprotection to provide compounds of the formula IQ. In a similar fashion, treatment of the protected amine with a compound having the formula $R^{13}SO_2X$, when X is chloro or bromo, followed by nitrogen deprotection, provides the corresponding sulfonamide derivative.

Other suitable amine protecting groups that can be used, alternatively, in the procedures described throughout this document include $-COCF_3$, $-COCCl_3$, $-COOCH_2CCl_3$, $-COO(C_1-C_6)$alkyl and $-COOCH_2C_6H_5$. These groups are stable under the conditions described herein, and may be removed by methods described for each in Greene's "Protective Groups in Organic Chemistry", referred to above.

Compounds of the formula I wherein R^1 is other than hydrogen can be prepared as described above, such as the reductive amination ring formation by which compound XXIV in Scheme 3 (R^1=benzyl) is formed, and by the methods described below. Compounds of the formula I wherein R^1 is hydrogen can be converted into the corresponding compounds wherein R^1 is other than hydrogen by treating them with an equivalent amount of an aldehyde (R^1CHO) or ketone (R^1R^1CO wherein the two R^1's are the same or different) and a reducing agent, preferably a hydride reagent such as sodium traicetoxyborohydride or sodium cyanoborohydride, in a solvent such as methylene chloride, tetrahydrofuran or dioxane. The addition of acid to facilitate the reaction may be necessary in some cases, and acetic acid is commonly used. The temperature of this reaction is typically ambient for a period of about 0.5 to 24 hours. Commonly used methods are described in J. Org. Chem. 1996, 61, 3849.

Compounds of the formula I wherein R^1 is other than hydrogen can also be prepared by subjecting the corresponding compounds wherein R^1 is hydrogen to an alkylation reaction, using methods well known to those of skill in the art. For example, the compound wherein R^1 is hydrogen is treated with an equivalent amount or an excess of R^1X, wherein R^1 is other than hydrogen and X is halo, preferably bromo or iodo, or an O-sulfate ester of R^1OH. This reaction is typically performed neat or in polar solvent such as water, dimethylformamide or dimethylsulfoxide, usually in the presence of base, such as but not limited to an alkyli metal carbonate, for instance. The temperature of the reaction will generally range from about 20-120°C (preferably, it will be about 100°C) for a period of about 0.1 to 24 hours.

Compounds of the formula I wherein R^1 is other than hydrogen can also be prepared by converting the corresponding compounds wherein R^1 is hydrogen into amides by reacting them with a compound of the formula $R^1C(=O)X$, wherein X is defined as above, using methods well known to those of skill in the art, and then reducing the resulting amide with

borane or lithium aluminum hydride. The reduction step is usually carried out in an ethereal solvent such as ethyl ether or THF at a temperature from about 20°C to about 70°C for about one to twenty hours, to produce the desired amine.

In each of the reactions discussed above, or illustrated in Schemes 1-13, above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, with ambient pressure, i.e., about 1 atmosphere, being preferred as a matter of convenience.

The compounds of the formula I and their pharmaceutically acceptable salts (hereafter "the active compounds") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These compounds are, most desirably, administered in dosages ranging from about 0.25 mg up to about 1500 mg per day, preferably from about 0.25 to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.01 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds can be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More particularly, the active compounds can be administered in a wide variety of different dosage forms, e.g., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic

acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc can be used for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar] as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration, a solution of an active compound in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

It is also possible to administer the active compounds topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Biological Assay

The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites is determined by the following procedure which is a modification of the methods of Lippiello, P. M. and Fernandes, K. G. (in The Binding of L-[^{3}H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes, Molecular Pharm., 29, 448-54, (1986)) and Anderson, D. J. and Arneric, S. P. (in Nicotinic Receptor Binding of ^{3}H-Cystisine, ^{3}H-Nicotine and ^{3}H-Methylcarmbamylcholine In Rat Brain, European J. Pharm., 253, 261-67 (1994)).

Procedure

Male Sprague-Dawley rats (200-300 g) from Charles River were housed in groups in hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.-7 p.m. light period). They received standard Purina Rat Chow and water *ad libitum*.

The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (Molec Pharmacol, 29, 448-454, (1986) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0° in 10 volumes of buffer (w/v) using a Brinkmann Polytron™, setting 6, for 30 seconds. The buffer consisted of 50 mM Tris HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10

minutes; 50,000 x g; 0 to 4°C. The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000 x g; 0 to 4°C. After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0g/100mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$ and has a pH of 7.4 at room temperature.

Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50µL of vehicle, blank, or test compound solution, respectively. To each tube was added 200 µL of [^{3}H]-nicotine in assay buffer followed by 750 µL of the membrane suspension. The final concentration of nicotine in each tube was 0.9 nM. The final concentration of cytisine in the blank was 1 µM. The vehicle consisted of deionized water containing 30 µL of 1 N acetic acid per 50 mL of water. The test compounds and cytisine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0 to 4° C in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B™ glass fiber filters using a Brandel™ multi-manifold tissue harvester. Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 m each). The filters were then placed in counting vials and mixed vigorously with 20 ml of Ready Safe™ (Beckman) before quantification of radioactivity. Samples were counted in a LKB Wallach Rackbeta™ liquid scintillation counter at 40-50% efficiency. All determinations were in triplicate.

Calculations

Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytisine (B), i.e.,

Specific binding = (C) = (A) - (B).

Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e., (E) = (D) - (B).

% Inhibition = (1-((E)/(C)) times 100.

The compounds of the invention that were tested in the above assay exhibited IC_{50} values of less than 10 µM.

The following experimental examples illustrate, but do not limit the scope of, this invention.

EXAMPLE 1

5,6-DIFLUORO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2,4,6-TRIENE HYDROCHLORIDE

A) Cyclopent-3-enyl-(2,3-difluoro-6-methoxy-phenyl)-methanol (For leading metalation references, see Example 6A. Cyclopent-3-enecarbaldehyde was derived from the lithium aluminum hydride reduction of cyclopent-3-enecarboxylic acid methoxy-methyl-amide, the preparation of which appears in Example 2A. For reduction conditions, see: Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M.; *J. Amer. Chem. Soc.* **1990**, *112*, 3475-3482.)

1,2-Difluoro-4-methoxy-benzene (10 g, 69.4 mmol) was stirred in anhydrous (anh.) THF (80 mL) in a dry 250 mL three neck round bottomed flask (3NRB flask) at -78 °C under nitrogen (N_2). To this was added n-butyllithium (n-BuLi) (28 mL, 2.5M/hexanes soln., 70 mmol) over 5 minutes. After stirring below -70 °C for 4.5 hours (h), a solution of cyclopent-3-enecarbaldehyde (5.7 g, 69.4 mmol) in anh. THF (30 mL) was added via addition funnel along the reaction vessel wall while keeping the internal temperature below -70 °C. After stirring for 1/2 hour (h), the reaction mixture was poured into a saturated aqueous ammonium chloride solution (sat. aq. NH_4Cl soln.) (100 mL), and the mixture was stirred and extracted with ethyl ether (Et_2O) (2 x 50 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed on silica gel to provide an oil (6.64 g, 40%). (Thin layer chromotography (TLC) 20%EtOAc/hexanes R_f 0.16). ^1H NMR ($CDCl_3$) δ 7.01 (ddd, J=9.0Hz, 1H), 6.58 (m, 1H), 5.72 (ddd, J=5.8,4.5,2.2 Hz, 1H), 5.62 (ddd, J=5.8,4.5,2.2 Hz, 1H), 4.79 (br d, J=9.5 Hz, 1H), 3.85 (s, 3H), 3.20 (br s, OH), 2.87 (m, 1H), 2.52 (AB m, 2H), 1.99 (AB m, 2H). GCMS m/e 240 (M^+).

B) 2-Cyclopent-3-enylmethyl-3,4-difluoro-1-methoxy-benzene (For related examples, see: Leeson, P. D.; Emmett, J. C.; Shah, V. P.; Showell, G. A.; Novelli, R. *J. Med. Chem.* **1989**, *32*, 320-336.)

Cyclopent-3-enyl-(2,3-difluoro-6-methoxy-phenyl)-methanol (6.64 g, 27.7 mmol) and triethylsilane (3.38 g, 29 mmol) were stirred in CH_2Cl_2 (40 mL) at 0°C. To this solution was added trifluoroacetic acid (17.3 mL, 224 mmol). The mixture was stirred at ambient temperature for 18 hours. The mixture was concentrated to an oil, which was dissolved in hexanes (100 mL), washed with water (H_2O) (2 x 50 mL) and a saturated aqueous sodium bicarbonate solution (sat. aq. $NaHCO_3$ soln.) (50 mL), and then dried (sodium sulfate (Na_2SO_4)), filtered, concentrated and chromatographed on Silica gel to provide an oil (3.67 g, 59%). (TLC hexanes R_f 0.38).

^{1}H NMR ($CDCl_3$) δ 6.92 (ddd, J=9.3 Hz, 1H), 6.49 (br d, J=9.3 Hz, 1H), 5.66 (br s, 2H), 3.78 (s, 3H), 2.72 (dd, J=7.5,2.0 Hz, 2H), 2.57 (m, 1H), 2.36 (AB m, 2H), 2.06 (AB dd, J=14.2,5.5 Hz, 2H). GCMS m/e 224 (M^+).

C) 2-Cyclopent-3-enylmethyl-3,4-difluoro-phenol

2-Cyclopent-3-enylmethyl-3,4-difluoro-1-methoxy-benzene (3.67 g, 16.38 mmol) and n-Bu_4NI (7.17 g, 19.4 mmol) were stirred in dry CH_2Cl_2 (50 mL) at -78 °C under nitrogen (N_2). To this was added boron trichloride (BCl_3) (22 mL, 1M CH_2Cl_2 soln., 22 mmol) over 2 minutes (min.). After 5 min., the solution was allowed to warm to room temperature (rt) and stirred for 2 hours. The reaction was quenched with H_2O (100 mL) and stirred for 1 hour. The layers were separated and the aq. layer extracted with methylene chloride (CH_2Cl_2) (2 x 30 mL). The combined organic layer was washed with H_2O (2 x 50 mL), and a sat. aq. $NaHCO_3$ soln. (50 mL), dried through a cotton plug, concentrated and chromatographed on silica gel to provide an oil (3.30 g, 96%). (TLC 50% ethyl acetate (EtOAc)/hexanes (hex) R_f 0.70). ^{1}H NMR ($CDCl_3$) δ 6.85 (ddd, J=9.0 Hz, 1H), 6.46 (m, 1H), 5.68 (br s, 2H), 4.76 (br s, 1H), 2.71 (d, J=8.0 Hz, 2H), 2.61 (m, 1H), 2.39 (AB m, 2H), 2.09 (AB dd, J=14.0,5.4 Hz, 2H). GSMS m/e 210 (M^+).

D) Trifluoro-methanesulfonic acid 2-cyclopent-3-enylmethyl-3,4-difluoro-phenyl ester

(For a leading reference, see: Su, T. M.; Sliwinski, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1969**, *91*, 5386.)

2-Cyclopent-3-enylmethyl-3,4-difluoro-phenol (3.30 g, 15.7 mmol) and pyridine (2.49 g, 31.5 mmol) were stirred in CH_2Cl_2 (50 mL) at -78 °C under N_2 and treated with trifluoromethane sulfonic anhydride (6.20 g, 22.0 mmol) dropwise over 20 min. The mixture was allowed to warm to rt and stirred for 1/2 hour then poured into 1N aq. HCl soln. and shaken. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with H_2O (50 mL), and a sat. aq. $NaHCO_3$ soln. (50 mL), dried through a cotton plug, concentrated and chromatographed on silica gel to provide an oil (4.34 g, 81%). (TLC 30%EtOAc/Hex R_f 0.60). ^{1}H NMR ($CDCl_3$) δ 7.13-7.03 (2H), 5.67 (br s, 2H), 2.82 (dd, J=7.5,2.0 Hz, 2H), 2.58 (m, 1H), 2.40 (dd, J=14.0,8.0 Hz, 2H), 2.05 (dd, J=14.0,5.5 Hz, 2H). GCMS *m/e* 342 (M^+).

E) 5,6-Difluorotricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene

Trifluoro-methanesulfonic acid 2-cyclopent-3-enylmethyl-3,4-difluoro-phenyl ester (340 mg, 0.99 mmol), was dissolved in DMF (5 mL) under a N_2 atmosphere and treated with diisopropylethylamine (0.26 mL, 1.5 mmol), potassium acetate (981 mg, 10.0 mmol) and tri-o-tolylphosphine (12 mg, 0.04 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles) and then treated with palladium acetate (5 mg, 0.02 mmol). After 20 min. the mixture was warmed to 100 °C for 18 hours, cooled and poured into brine (50 mL). The

resulting mixture was extracted with hexanes (4 x 25 mL) and the combined organic layer was washed with a sat. aq. $NaHCO_3$ soln. (10 mL), water (H_2O) (10 mL), brine (10 mL), dried (magnesium sulfate ($MgSO_4$)), filtered and and chromatographed on silica gel to provide an oil (110 mg, 60%). (TLC hexanes R_f 0.58). ^1H NMR ($CDCl_3$) δ 6.80 (ddd, J=6.6,8.1,8.3 Hz, 1H), 6.68 (m, 1H), 6.17 (dd, J=5.5,2.8 Hz, 1H), 5.77 (dd, J=5.5,2.8 Hz, 1H), 3.29 (br s, 1H), 2.96 (br s, 1H), 2.84 (AB dd, J=17.9,5.0 Hz, 1H), 2.54 (AB d, J=17.9 Hz, 1H), 2.19 (m, 1H), 1.77 (d, J=10.5 Hz, 1H). GCMS m/e 192 (M^+).

F) 5,6-Difluoro-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5-triene

5,6-Difluorotricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (714 mg, 3.72 mmol) and N-methyl morpholine N-oxide (553 mg, 4.10 mmol) were stirred in acetone (20 mL) and H_2O (3 mL). To this was added a solution of osmium tetraoxide (OsO_4) (0.2 mL, 2.5%wt. soln. in t-butanol (t-BuOH), 0.02 mmol). After 18 hours, the mixture was concentrated to an oil, dissolved in a minimum of CH_2Cl_2 and filtered through a silica pad (3 x 3 mm) eluting with 20% EtOAc/hexanes. Product containing fractions were concentrated to an oil (850 mg, 100%). (TLC 20% EtOAc/hexanes R_f 0.37). ^1H NMR ($CDCl_3$) δ 6.88 (ddd, J=9.3,8.5,7.6 Hz, 1H), 6.78 (m, 1H), 4.01 (AB d, 2H), 3.06 (br s, 1H), 2.92 (AB dd, J=17.9,5.0 Hz, 1H), 2.75 (br AB, J=17.9 Hz, 1H), 2.44 (br s, 1H), 2.32 (2-OH), 2.26 (m, 1H), 1.50 (d, J=7.8 Hz, 1H). GCMS m/e 226 (M^+).

G) 5,6-Difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

5,6-Difluoro-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5-triene (840 mg, 3.72 mmol) was stirred in a parr bottle in ethanol (EtOH) (30 mL) and H_2O (10 mL). To this a soln. of sodium periodate ($NaIO_4$) (810 mg, 3.72 mmol) in H_2O (5 mL) was added. The resulting milky white dispersion was stirred 15 min., then treated with 37% aq. ammonium hydroxide (NH_4OH) soln. (25 mL) and palladium hydroxide ($Pd(OH)_2$) (360 mg, 20%wt/C) and shaken under 45 psi of H_2. After 18 hours, the mixture was filtered through a Celite pad and rinsed with EtOH and a 3:1 ethanol: water mixture. The filtrate was concentrated to an oily solid which was dissolved in EtOAc (50 mL) and washed with sat. aq. sodium carbonate (Na_2CO_3) soln. (2 x 20 mL). The organic layer was dried sodium sulfate (Na_2SO_4)), filtered, concentrated and chromatographed on Silica gel to provide an oil (330 mg, 42%). (TLC 5%MeOH/CH_2Cl_2 R_f 0.36). ^1H NMR ($CDCl_3$) δ 6.92 (ddd, J=8.1,8.5,10.0 Hz, 1H), 6.74 (m, 1H), 3.02-2.93 (4H), 2.83-2.71 (3H), 2.09 (br s, 1H), 1.98 (br d, J=12.5 Hz, 1H), 1.82 (br d, J=12.5 Hz, 1H). GSMS m/e 209 (M^+). APCI MS m/e 209.8 [$(M+1)^+$].

The product was dissolved in methanol (CH_3OH) and treated with 3M hydrochloric acid (HCl)/EtOAc (3 ml). The resulting slurry was concentrated, dissolved in a minimum of MeOH, saturated with Et_2O and stirred for 18 hours. The solids were filtered to give white solid (335 mg, 86%). mp 290-305 °C.

EXAMPLE 2

11-BENZYL-6-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) Cyclopent-3-enecarboxylic acid methoxy-methyl-amide (For preparation of cyclopent-3-enecarboxylic acid, see: Depres, J-P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928-931, and for more recent approaches, see: a) Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992-8998, and b) Marinez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963-7966. For related methods for amide formation, see: Nitz, T. J.; Volkots, D. L.; Aldous, D. J.; Oglesby, R. C. *J. Org. Chem.* **1994**, *59*, 5823-5832.)

Cyclopent-3-enecarboxylic acid (65.6 g, 586 mmol) in CH_2Cl_2 (1 L) was treated with carbonyl diimidazole (100 g, 617 mmol) in portions. After ~3/4 h, the resulting solution was treated with N,O-dimethylhydroxylamine (60.8 g, 623 mmol) and the mixture was stirred for 40 h. The reaction was quenched with 1N aq. HCl soln. (600 mL), shaken and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with 1N aq. HCl soln. (100 mL), H_2O (2 x 150 mL), 50% sat. aq. Na_2CO_3 soln./brine (200 mL) and dried through a cotton plug. The filtrate was diluted with EtOAc to ~10%EtOAc/CH_2Cl_2 and filtered through a silica pad (10 x 10 mm) eluting with 10%EtOAc/ CH_2Cl_2 to remove baseline color. Concentration affords a liquid (86 g, 95%). (TLC 10%EtOAc/ CH_2Cl_2 R_f 0.56). ^{1}H NMR ($CDCl_3$) δ 5.64 (br s, 2H), 3.69 (s, 3H), 3.47 (m, 1H), 3.19 (s, 3H), 2.61 (m, 4H). GSMS m/e 155 (M^+).

B) Cyclopent-3-enyl-(2,6-dimethoxy-phenyl)-methanone (For a leading reference, see: Koft, E. R.; Smith, A. B.. III. *J. Am. Chem. Soc.* **1982**, *104*, 2659.)

1,3-Dimethoxybenzene (31.9 g, 231 mmol) was stirred in anh. Et_2O (200 mL) at 0°C under N_2 and treated with n-butyllithium (n-BuLi) (92.5 mL, 2.5M/hexanes soln., 231 mmol) over 5 minutes. The solution was brought to reflux for 4h, then cooled to -78 °C. The slurry was treated with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (35.9 g, 231 mmol) dropwise over ~1 hour, then the mixture was stirred for 18 hours (the cooling bath evaporated overnight). The mixture was poured into 1N aq. HCl soln. (200 mL) and shaken. The layers were separated and the aq. layer extracted with Et_2O (2 x 100 mL). The organic layer was washed with H_2O (50 mL), and a sat. aq. $NaHCO_3$ soln. (100 mL), dried (Na_2SO_4), filtered through a silica plug and concentrated to an oil (52.6 g, 98%). (TLC 10%EtOAc/hexanes R_f 0.25). ^{1}H NMR ($CDCl_3$) δ 7.24 (t, J=8.4 Hz, 1H), 6.24 (d, J=8.4 Hz, 2H), 5.63 (br s, 2H), 3.76 (s, 6H), 3.68 (m, 1H), 2.75 (m, 2H), 2.48 (m, 2H). GSMS m/e 232 (M^+).

C) Cyclopent-3-enyl-(2-hydroxy-6-methoxy-phenyl)-methanone (For a leading reference, see: Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899.)

Cyclopent-3-enyl-(2,6-dimethoxy-phenyl)-methanone (52.6 g, 226 mmol) was stirred in CH_2Cl_2 (200 mL) at -78 °C under N_2 and treated with boron trichloride (BCl_3) (273 mL, 1M CH_2Cl_2 soln., 273 mmol) over 30 min. The mixture was allowed to warm to ambient temperature and was treated with additional BCl_3 (41.0 mL, 1M CH_2Cl_2 soln., 41.0 mmol). After the mixture was stirred 20 min., it was poured slowly into H_2O (300 mL) and stirred for 30 min. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with H_2O (3 x 100 mL), sat. aq. $NaHCO_3$ soln. (100 mL), dried through a cotton plug and filtered through a Silica pad to remove baseline color. Concentration affords an amber oil (46.0 g, 93%). (TLC 10%EtOAc/hexanes R_f 0.50). ^1H NMR ($CDCl_3$) δ 7.32 (t, J=8.5 Hz, 1H), 6.57 (dd, J=8.5,1.0 Hz, 1H), 6.38 (dd, J=8.5,1.0 Hz, 1H), 5.66 (br s, 2H), 4.31 (m, 1H), 3.89 (s, 3H), 2.80-2.63 (4H). GSMS m/e 218 (M^+).

D) Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-3-methoxy-phenyl ester Cyclopent-3-enyl-(2-hydroxy-6-methoxy-phenyl)-methanone (45.0 g, 206 mmol) and pyridine (36.0 g, 453 mmol) were stirred in CH_2Cl_2 (250 mL) at -78 °C under N_2. To this a solution of trifluoromethane sulfonic anhydride (75.7 g, 268 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1/2 h. The mixture was allowed to warm to ambient temperature, stirred 1h, then poured into 1N aq. HCl soln. (250 mL). The mixture was shaken, the layers were separated, and the organic layer was washed with 1N aq. HCl soln. (3 x 150 mL), H_2O (2 x 100 mL), sat. aq. $NaHCO_3$ soln. (100 mL) and finally brine (100 mL). The organic layer was dried through a cotton plug and concentrated to an oil which was chromatographed through a Silica gel plug eluting with 10%EtOAc/hexanes to afford after concentration an oil (62.5 g, 87%). (TLC 10%EtOAc/hexanes R_f 0.14). ^1H NMR ($CDCl_3$) δ 7.41 (t, J=8.5 Hz, 1H), 6.95 (dd, J=8.5,1.0 Hz, 2H), 5.64 (br s, 2H), 3.86 (s, 3H), 3.73 (m, 1H), 2.70 (m, 2H), 2.57 (m, 2H). GSMS m/e 350 (M^+).

E) 6-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8-one (For leading references, see: Heck, R. F. *Org. React.* (N.Y.) **1982**, *27*, 345, and Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2-7.)

Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-3-methoxy-phenyl ester (45.0 g, 129 mmol) was dissolved in DMF (100 mL) under a N_2 atmosphere and treated with triethylamine (19.5 g, 193 mmol), potassium acetate (1.89 g, 19.0 mmol) and 1,3-bis(diphenylphosphino)propane (5.30 g, 12.9 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles) then treated with palladium acetate (1.16 g, 5.14 mmol). After 20 min. the mixture was warmed to 130 °C for 1 hour, cooled and poured into brine (300 mL). The resulting mixture was extracted with EtOAc (4 x 100 mL) and the combined organic layer

was washed with sat. aq. $NaHCO_3$ soln. (100 mL), H_2O (100 mL), and brine (100 mL), dried ($MgSO_4$), filtered and evaporated to an oil. (55 g). The oil was chromatographed on silica gel to provide product as a white solid (12.0 g, 47%). (TLC 25%EtOAc/ hexanes R_f 0.27). ^1H NMR ($CDCl_3$) δ 7.29 (t, J=8.0 Hz, 1H), 6.84 (d, J=8.0 Hz, 1H), 6.73 (d, J=8.0 Hz, 1H), 6.63 (dd, J=5.0,3.0 Hz, 1H), 6.15 (dd, J=5.0,3.0 Hz, 1H), 3.87 (s, 3H), 3.60 (br s, 1H), 3.39 (br s, 1H), 2.56 (AB m, 2H). ^{13}C NMR 195.38, 161.61, 149.82, 143.47, 133.77, 131.84, 131.80, 117.51, 111.46, 57.63, 55.96, 47.63, 47.51. GSMS m/e 200 (M^+). mp 135-136 °C.

F) 6-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (For a discussion, see: Fieser and Fieser, *Reagents for Organic Synthesis*, (N.Y.) **1967**, *1*, p.435.)

6-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8-one (3.0 g, 15 mmol) and pulverized KOH (5.05 g, 90 mmol) were warmed in ethylene glycol (40 mL) until solution occurred. The mixture was cooled to room temperature, treated with hydrazine hydrate (3.0 g, 60 mmol) and heated to reflux for 2 hours. The reflux condenser was replaced with a distilling head and distillates were collected from 120-190 °C. These distillates were diluted with H_2O (100 mL) and extracted with EtOAc (4 x 40 mL). The organic layer was washed with H_2O (4 x 30 mL), and brine (25 mL), dried ($MgSO_4$), filtered and concentrated to an oil (2.68 g, 96%). (TLC 50%EtOAc/ hexanes R_f 0.67). ^1H NMR ($CDCl_3$) δ 7.18 (t, J=8.0 Hz, 1H), 6.82 (d, J=8.0 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 6.32 (dd, J=5.0,3.0 Hz, 1H), 5.93 (dd, J=5.0,3.0 Hz, 1H), 3.91 (s, 3H), 3.45 (dd, J=5.0,1.5 Hz, 1H), 3.11 (br s, 1H), 2.88 (AB dd, J=17.0,5.0 Hz, 1H), 2.58 (AB d, J=17.0 Hz, 1H), 2.31 (m, 1H), 1.96 (d, J=9.5 Hz, 1H).

G) 6-Methoxy-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-triene

6-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (1.5 g, 8.19 mmol) and N-methyl morpholine N-oxide (1.06 g, 9.03 mmol) were stirred in acetone (20 mL) and H_2O (0.16 mL). To this was added a solution of osmiom tetraoxide (OsO_4) (0.2 mL, 2.5%wt. soln. in t-butanol (t-BuOH), 0.02 mmol). After 2 hours, the mixture was diluted with EtOAc (50 mL) and washed with 10%aq. $NaHSO_3$ soln. (30 mL), H_2O (2 x 30 mL), sat. aq. $NaHCO_3$ soln. (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to an oil (1.79 g, 99%). (TLC 50%EtOAc/hexanes R_f 0.20).

H) 11-Benzyl-6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (For a discussion of oxidative cleavage with $Pb(OAc_4)$, see: Fieser and Fieser, *Reagents for Organic Synthesis*, (N.Y.) **1967**, *1*, p.549. For reductive amination conditions and references, see Abdel-Magid et al. , *J. Org. Chem.*, **1996**, *61*, 3849; and Mazzocchi et al., *J. Med. Chem.*, **1979**, *22*, 455.)

1-Methoxy-6,7,8,9-tetrahydro-5H-5,8-methano-benzocycloheptene-6,7-diol (2.40 g, 11.0 mmol) was stirred at 0 °C in CH_2Cl_2 (70 mL) and treated with $Pb(OAc)_4$ (5.08 g, 11.5 mmol). After 2 hours the mixture was filtered through a Celite pad and rinsed with CH_2Cl_2

(10 mL). To the stirred filtrate was added acetic acid (AcOH) (1.97 g, 33.0 mmol) and benzyl amine (1.23 g, 11.5 mmol). After 15 min., the mixture was treated with sodium triacetoxyborohydride ($NaBH(OAc)_3$) (6.94 g, 33.0 mmol) and stirred for 18 hours. The mixture was poured into a sat. aq. $NaHCO_3$ soln. (100 mL) and stirred for 1/2 hour. The layers were separated and extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was washed with a saturated (sat.) aqueous (aq.) sodium bicarbonate ($NaHCO_3$) soln. (2 x 50 mL), H_2O (50 mL), brine (50 mL), dried through a cotton plug, concentrated and purified by chromatography on Silica gel eluting with 10%EtOAc/hexanes to provide product as an oil (1.45 g, 45%). (TLC 25%EtOAc/hexanes R_f 0.76). ^1H NMR ($CDCl_3$) δ 7.12 (m, 4H), 6.89 (m, 2H), 6.74 (d, J=8.0 Hz, 1H), 6.64 (d, J=8.0 Hz, 1H), 3.87 (s, 3H), 3.41 (AB d, J=14.2 Hz, 1H), 3.38 (AB d, J=14.2 Hz, 1H), 2.87-2.70 (m, 5H), 2.36-2.23 (m, 3H), 1.85 (br AB d, J=12.1 Hz, 1H), 1.77 (br AB d, J=12.1 Hz, 1H). This oil was dissolved in a minimum of methanol (MeOH), stirred, and saturated with Et_2O. After 18 hours the white solids were filtered. ^1H NMR (CD_3OD) δ 7.44 (m, 5H), 7.15 (t, J=8.0 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 4.27 (AB d, J=13.0 Hz, 1H), 4.15 (AB d, J=13.0 Hz, 1H), 3.84 (s, 3H), 3.47 (br d , J=12.3 Hz, 1H), 3.36-3.19 (m, 4H), 2.98 (AB dd, J=18.7,7.2 Hz, 1H), 2.85 (AB d, J=18.7 Hz, 1H), 2.60 (br s, 1H), 2.00 (AB d, J=13.0 Hz, 1H), 1.87 (AB d, J= 13.0 Hz, 1H). mp 210-212 °C

EXAMPLE 3

6-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (525 mg, 1.64 mmol), ammonium formate (2.07 g, 32.0 mmol) and 10% palladium hydroxide on carbon ($Pd(OH)_2/C$) (200 mg) were combined in MeOH (30 mL) and refluxed for 2 hours. The mixture was filtered hot through Celite and the filtrate concentrated then azeotroped from MeOH (5 x 50 mL) to yield a solid. This was recrystallized from MeOH/Et_2O to provide a white solid (306 mg, 81%). ^1H NMR (free base, $CDCl_3$) δ 7.15 (t, J=8.0 Hz, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.63 (d, J=8.0 Hz, 1H), 3.82 (s, 3H), 3.34 (br d, J=13.0 Hz, 1H), 3.11-3.02 (m, 4H), 2.94 (AB d, J=18.3 Hz, 1H), 2.87 (AB dd, J=18.3,6.5 Hz, 1H), 2.41 (br s, 1H), 1.91 (AB q, 2H). GSMS m/e 203 (M^+). mp 272-274 °C.

EXAMPLE 4

11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-6-OL

6-Methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (55 mg, 0.23 mmol) was brought to reflux in 48% aq. hydrobronic acid (HBr) (5 mL). After 1 hour the solution was cooled and poured into 1N aq. NaOH soln. adjusted to pH 10 and product was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to a white solid, which was recrystallized from EtOAc/hexanes (20

mg, 46%). ^{1}H NMR ($CDCl_3$) δ 6.95 (t, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 6.53 (d, J=8.0 Hz, 1H), 3.27 (m, 1H), 3.11 (m, 2H), 3.02 (m, 2H), 2.77 (m, 1H), 2.57 (m,1H), 2.33 (br s, 1H), 1.90 (m, 2H). mp 106-108 °C.

EXAMPLE 5

6-FLUORO-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

3-Fluoromethoxybenzene (15.8 g, 125 mmol) was stirred at -78 °C in anh. THF (100 mL) and treated with n-BuLi (50 mL, 2.5M hexanes soln., 125 mmol) over 5 min. After stirring below –70 °C for 4 hours, the mixture was treated with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (18.4 g, 119 mmol) dropwise over ~1/4 hour. The mixture was stirred below –70 °C for 1 hour, and then allowed to warm to ambient temperature over ~1 hour. The mixture was poured into 1N aq. HCl soln. (200 mL) and shaken. The layers were separated and the aq. layer extracted with EtOAc (3 x 100 mL). The organic layer was washed with H_2O (50 mL), sat. aq. $NaHCO_3$ soln. (100 mL), and brine (50 mL), dried (Na_2SO_4), filtered through a Silica plug and concentrated to an oil (21.0 g, 76%). (TLC 30%EtOAc/ hexanes R_f 0.43). GCMS *m/e* 220 (M^+). This material was converted to the title compound by the methods described in Example 2C-G and Example 1G. (TLC 10%MeOH/CH_2Cl_2 (NH_3) R_f 0.20). ^{1}H NMR (CD_3OD) δ 7.24 (m, 1H), 7.01 (m, 2H), 3.36 (d, J=13.0 Hz, 1H), 3.33-3.10 (m, 5H), 2.90 (d, J=18.5 Hz, 1H), 2.60 (m, 1H), 2.13 (AB d, J=13.0 Hz, 1H), 1.97 (AB d, J= 13.0 Hz, 1H). mp 240-241 °C.

EXAMPLE 6

11-BENZYL-5-METHOXY-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) Cyclopent-3-enyl-(2,5-dimethoxy-phenyl)-methanone (For a discussion of halogen-metal exchange, see: Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.)

2-Bromo-1,4-dimethoxy-benzene (42.2 g, 195 mmol) was stirred in Et_2O (200 mL) under N_2 at -78 °C. The resulting precipitate was dissolved by the addition of THF (50 mL). To the resulting solution was added n-BuLi (78 mL, 2.5M in hexanes, 195 mmol) over 10 min. After stirring 10 min., the yellow solution was treated with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (29.15 g, 188 mmol) in Et_2O (50 mL) over 10 min., then the mixture was stirred for 18 hours (the cooling bath evaporated overnight). The mixture was poured into 10% aq. HCl soln. (400 mL) and shaken. The layers were separated and the aq. layer extracted with Et_2O (3 x 50 mL). The organic layer was washed with H_2O (50 mL), a sat. aq. $NaHCO_3$ soln. (100 mL), dried (Na_2SO_4), filtered through a silica plug and concentrated to an oil (43.0 g, 99%). (In a separate experiment, THF was successfully

substituted for Et_2O in the reaction above.) (TLC 10%EtOAc/hexanes R_f 0.39). ^1H NMR ($CDCl_3$) δ 7.16 (d, J=3.0 Hz, 1H), 6.98 (dd, J=9.0,3.0 Hz, 1H), 6.88 (d, J=9.0 Hz, 1H), 5.64 (br s, 2H), 4.11 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.66 (m, 4H).

B) Cyclopent-3-enyl-(2-hydroxy-5-methoxy-phenyl)-methanone

Cyclopent-3-enyl-(2,5-dimethoxy-phenyl)-methanone (40.0 g, 172 mmol) was converted to the title compound as described in Example 2C to provide an oil (39.5 g, crude). (TLC 10%EtOAc/hexanes R_f 0.50). ^1H NMR ($CDCl_3$) δ 7.21 (m, 1H), 7.10 (m, 1H), 6.93 (br d, J=9.0 Hz, 1H), 5.69 (br s, 2H), 4.06 m, 1H), 3.79 (s, 3H), 2.76 (m, 4H). GCMS *m/e* 218 (M^+).

C) Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-4-methoxy-phenyl ester

Cyclopent-3-enyl-(2-hydroxy-5-methoxy-phenyl)-methanone (39.5 g crude, 172 mmol) and pyridine (28.7 g, 362 mmol) were stirred in CH_2Cl_2 (300 mL) at -78 °C under N_2. To this a solution trifluoromethane sulfonic anhydride (63.8 g, 226 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1/2 hour. The mixture was allowed to warm to ambient temperature and stirred 1h then poured into a 1N aq. HCl soln. (250 mL). The mixture was shaken, the layers were separated, and the organic layer was washed with a1N aq. HCl soln. (3 x 150 mL), H_2O (2 x 100 mL), a sat. aq. $NaHCO_3$ soln. (100 mL) and, finally, brine (100 mL). The organic layer was dried through a cotton plug and concentrated to an oil which was chromatographed through a Silica gel plug eluting with 10%EtOAc/hexanes to afford after concentration an oil (55.7 g, 93% over 2 steps). GCMS *m/e* 350 (M^+).

D) 5-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8-one

Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-4-methoxy-phenyl ester (19.09 g, 54.5 mmol) was dissolved in DMF (100 mL) under a N_2 atmosphere and treated with diisopropylethylamine (10.6 g, 82.0 mmol), potassium acetate (1.07 g, 11.0 mmol) and 1,3-bis(diphenylphosphino)propane (2.25 g, 5.46 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles) then treated with palladium acetate (0.49 g, 2.18 mmol). After stirring 20 min. the mixture was warmed to 120 °C for 18 hours, cooled and poured into brine (300 mL). The resulting mixture was extracted with EtOAc (4 x 100 mL) and the combined organic layer was washed with a sat. aq. $NaHCO_3$ soln. (100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel to provide an oil (10.4 g, 95%). (elute w/ 7%EtOAc/hexanes). ^1H NMR ($CDCl_3$) δ 7.41 (d, J=2.8 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 6.88 (dd, J=8.0,2.8 Hz, 1H), 6.72 (dd, J=5.2,3.0 Hz,1H), 6.06 (dd, J=5.2,3.2 Hz, 1H), 3.77 (s, 3H), 3.60 (dd, J=4.3,3.2 Hz, 1H), 3.44 (dd, J=5.0,3.4 Hz, 1H), 2.65 (AB m, 1H), 2.56 (br AB d, J=10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 196.11, 158.87, 145.90, 140.34, 130.295, 129.94, 126.14, 119.42, 111.90, 55.61, 55.48, 49.08, 45.97. GCMS *m/e* 200 (M^+).

E) 5-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene

5-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8-one (9.41 g, 47 mmol) and pulverized potassium hydroxide (KOH) (6.17 g, 110 mmol) were warmed in ethylene glycol (50 mL) until solution occurred. The mixture was cooled to rt, treated with hydrazine hydrate (6 mL, 190 mmol) and heated to reflux for 2 hours. The reflux condenser was replaced with a distilling head and distillates were collected from 120-190 °C. The distillates were diluted with H_2O (100 mL) and extracted with EtOAc (4 x 40 mL). The organic layer was washed with H_2O (4 x 30 mL), brine (25 mL), dried ($MgSO_4$), filtered and concentrated to an oil (8.2 g, 94%). (TLC 25%EtOAc/ hexanes R_f 0.68). ^{1}H NMR ($CDCl_3$) δ 6.92 (d, J=8.0 Hz, 1H), 6.88 (m, 2H), 6.25 (dd, J=5.1,2.5 Hz, 1H), 5.79 (dd, J=5.1,2.4 Hz, 1H), 3.77 (s, 3H), 3.31 (br s, 1H), 3.01-2.94 (2H), 2.56 (d, J=16.5 Hz, 1H), 2.22 (m, 1H), 1.85 (d, J=10.0 Hz, 1H). GCMS *m/e* 186 (M^+).

F) 5-Methoxy-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-triene

5-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (6.66 g, 35.7 mmol) was converted to the title compound as described in Example 2G to provide an oil (7.86 g, 100%). (TLC 10%MeOH/CH_2Cl_2 R_f 0.44). ^{1}H NMR ($CDCl_3$) δ 6.95 (d, J=8.0 Hz, 1H), 6.63 (dd, J=8.0,2.5 Hz, 1H), 6.56 (br s, 1H), 4.00 (s, 3H), 3.77 (m, 3H), 3.04-2.99 (m, 2H), 2.69 (d, J=13.0 Hz, 1H), 2.41 (br s, 1H), 2.33 (br s, 1H), 2.22 (m, 1H), 1.52 (d, J=11.5 Hz, 1H).

G) 11-Benzyl-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

5-Methoxy-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-triene (18.0 g, 79.0 mmol) was stirred at 0 °C in CH_2Cl_2 (150 mL) and treated with lead tetraacetate ($Pb(OAc)_4$) (35.0 g, 79.0 mmol). After 30 min. the mixture was filtered through a Celite pad and rinsed with CH_2Cl_2 (50 mL). To the stirred filtrate was added AcOH (23.7 g, 395 mmol) and benzyl amine (8.50 g, 79.0 mmol). After 15 min., the mixture was treated with $NaBH(OAc)_3$ (50.2 g, 237 mmol) and stirred for 18 hours. The mixture was poured into a sat. aq. Na_2CO_3 soln. (100 mL) stirred for 1/2 hour. The layers were separated and extracted with CH_2Cl_2 (2 x 100 mL). The organic layer was washed with a sat. aq. Na_2CO_3 soln. (2 x 50 mL), H_2O (50 mL), and then brine (50 mL), dried through a cotton plug and concentrated to an oil. Chromatography on silica gel eluting with 5%EtOAc/hexanes provided product as an oil (9.48 g, 41%). (TLC 25%EtOAc/hexanes R_f 0.69). ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 3H), 6.92 (m, 3H), 6.71 (br s, 1H), 6.67 (dd, J=8.0,2.5 Hz, 1H), 3.83 (s, 3H), 3.99 (s, 2H), 3.07 (AB dd, J=17.5,7.0 Hz, 1H), 2.85 (br s, 1H), 2.83 (m, 1H), 2.79 (AB d, J=17.5 Hz, 1H), 2.70 (br d, J=10.5 Hz, 1H), 2.35 (dd, J=10.5,2.0 Hz, 1H), 2.27 (dd, J=10.2,2.0 Hz, 1H), 2.15 (br s, 1H), 1.86 (AB d, J=12.3 Hz, 1H), 1.78 (AB d, J=12.3 Hz, 1H). GCMS *m/e* 293 (M^+). This material was dissolved in excess 1N HCl MeOH and concentrated. The solids were dissolved in a

minimum of MeOH, stirred, and saturated with Et_2O. After stirring 18h the white solids were filtered (900 mg, 58%). ^1H NMR (CD_3OD) δ 7.40 (m, 5H), 7.00 (d, J=8.0 Hz, 1H), 6.73 (m, 2H), 4.28 (AB d, J=13.5 Hz, 1H), 4.16 (AB d, J=13.5 Hz, 1H), 3.76 (s, 3H), 3.48 (br d , J=12.0 Hz, 1H), 3.35-3.20 (m, 5H), 2.98 (AB d, J=18.4 Hz, 1H), 2.54 (br s, 1H), 2.01 (AB d, J=12.0 Hz, 1H), 1.89 (AB d, J= 12.0 Hz, 1H). mp 233-234 °C.

EXAMPLE 7

11-BENZYL-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-5-OL HYDROCHLORIDE

11-Benzyl-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene (203 mg, 0.62 mmol) was brought to reflux in 48%HBr (5 mL). After 1 hour the solution was cooled and poured into an aq. NH_4OH soln., the pH was adjusted to ~9 and the product was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to an oil. (TLC 25%EtOAc/hexanes (NH_3) R_f 0.37). This material was dissolved in excess 1N HCl in MeOH and concentrated. Recrystallization from MeOH/Et_2O provided a solid (154 mg, 80%). ^1H NMR ($CDCl_3$) δ 7.42 (m, 5H), 6.90 (d, J=8.0 Hz, 1H), 6.60 (m, 2H), 4.27 (AB d, J=13.0 Hz, 1H), 4.15 (AB d, J=13.0 Hz, 1H), 3.47 (d, J=12.2 Hz, 1H), 3.33-3.15 (5H), 2.86 (d, J=18.0 Hz, 1H), 2.52 (br s, 1H), 1.99 (AB d, J=12.5 Hz, 1H), 1.88 (AB d, J=12.5 Hz, 1H). mp 251-253 °C.

EXAMPLE 8

5-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (206 mg, 0.63 mmol) was converted to the title compound by the method described in Example 3 to provide a white solid (122 mg, 81%). (TLC 10 %MeOH/CH_2Cl_2 (NH_3) R_f 0.48). ^1H NMR (CD_3OD) δ 7.08 (d, J=8.0 Hz, 1H), 6.77 (m, 2H), 3.76 (s, 3H), 3.31-3.12 (m, 6H), 2.98 (AB d, J=18.4 Hz, 1H), 2.43 (br s, 1H), 2.10 (AB d, J=13.0 Hz, 1H), 1.94 (AB d, J= 13.0 Hz, 1H). GSMS m/e 203 (M^+). mp 253.5-256 °C.

EXAMPLE 9

11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-5-OL HYDROCHLORIDE

5-Methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (187 mg, 0.78 mmol) was brought to reflux in 48%HBr (5 mL). After 1 hour the solution was cooled and poured into aq. NH_4OH soln., the pH was adjusted to ~9 and the product was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to a solid. (TLC 10 %MeOH/CH_2Cl_2 (NH_3) R_f 0.13). This material was dissolved in excess 1N HCl MeOH and concentrated. Recrystallization from MeOH/Et_2O provided a solid (70 mg, 40%). ^1H NMR (CD_3OD) δ 6.99 (d, J=8.0 Hz, 1H), 6.63 (m, 2H),

3.48-3.11 (6H), 2.83 (d, J=18.0 Hz, 1H), 2.42 (br s, 1H), 2.08 (AB d, J=12.5 Hz, 1H), 1.93 (AB d, J= 12.5 Hz, 1H). mp 295-298 °C.

EXAMPLE 10

11-BENZYL-5-DIFLUOROMETHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE (For leading references, see: Langlois, B. R. *J. Fluorine Chem.* **1988**, *41*, 247-262.)

11-Benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol (572 mg, 2.05 mmol) was stirred in dioxane (5 mL) and H_2O (1 mL) at reflux under a balloon of freon (HCF_2Cl). To this was added 3N KOH dropwise so as to maintain a pH~12. The consumption of starting material was monitored by TLC for over 2 hours. The reaction was cooled, diluted with H_2O (40 mL) and extracted with EtOAc. The organic layer was washed with a sat. aq. Na_2CO_3 soln. (25 mL) and brine (25 mL), dried ($MgSO_2$), filtered and concentrated to an oil (620 mg, 92%). GCMS *m/e* 329 (M^+).

EXAMPLE 11

5-DIFLUOROMETHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-5-difluoromethoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene (620 mg, 1.88 mmol) was converted to the title compound as described in Example 3. The HCl salt was generated as in Example 9 to provide product as a white powder (280 mg, 54%). ^1H NMR ($CDCl_3$) δ 7.42 (m, 5H), 7.01 (d, J=9.0 Hz, 1H), 6.92 (m, 2H), 6.48 (t, J=74 Hz, 1H), 3.37 (d, J=13.0 Hz, 1H), 3.18-3.04 (6H), 2.39 (br s, 1H), 1.95 (br s, 2H). GCMS *m/e* 239 (M^+). mp 230-234 °C.

EXAMPLE 12

11-BENZYL-5-ETHYL-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE (For a review, see: Mitsunobu, O. *Synthesis*, **1981**, 1.)

11-Benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol (208 mg, 0.75 mmol), ethanol (69 mg, 1.49 mmol) and triphenylphosphine (391 mg, 1.49 mmol) were stirred under N_2 at 0°C in THF (2.5 mL). To this was added diethylazodicarboxylate (259 mg, 1.49 mmol) dropwise. After 18 hours, the reaction was concentrated, diluted with Et_2O (20 mL) and extracted with 1% aq. phosphoric acid (H_3PO_4) soln. (3 x 20 mL). The combined aq. layer was extracted with Et_2O (10 mL) and then basified to pH 10 with 1N NaOH soln. Product was extracted with EtOAc (3 x 20 mL) and the combined organic layer was washed with 1N NaOH soln. (20 mL) and brine (20 mL). The solution was dried ($MgSO_4$), filtered and evaporated to an oil (170 mg, 74%). (TLC 17%EtOAc/hexanes (NH_3) R_f 0.76). ^1H NMR ($CDCl_3$) δ 7.12 (m, 3H), 6.91 (m, 2H), 6.86 (d, J=8.0 Hz, 1H), 6.68 (br s, 1H), 6.63 (dd,

J=8.0,2.5 Hz, 1H), 4.03 (q, 2H), 3.37 (br s, 2H), 3.03 (dd, J=17.0,7.0 Hz, 1H), 2.82-2.68 (4H), 2.18 (2H), 2.12 (br s, 1H), 1.83 (AB d, J=12.0 Hz, 1H), 1.75 (AB d, J=12.0 Hz, 1H), 1.43 (t, J=7.0 Hz, 3H). GCMS *m/e* 307 (M^+). This material was dissolved in excess 1N HCl MeOH and concentrated. Recrystallization from CH_2Cl_2/Et_2O provided a solid (185 mg, 97%). mp 200-203 °C.

EXAMPLE 13

5-ETHYL-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-5-Ethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (160 mg, mmol), ammonium formate (220 mg, 3.49 mmol) and 10%$Pd(OH)_2$/C (100 mg) were combined in methanol (MeOH) (5 mL) and warmed to reflux for 15 min. The mixture was cooled, filtered, concentrated, diluted with sat. aq. Na_2CO_2 soln. and extracted with EtOAc (3 x 20 mL). The extracts were dried ($MgSO_4$), filtered and concentrated to an oil (94 mg, 83%). (TLC 50%EtOAc/hexanes (NH_3) R_f 0.20). ^{1}H NMR ($CDCl_3$) δ 6.90 (d, J=9.0 Hz, 1H), 6.66 (2H), 3.97 (m, 2H), 3.08 (dd, J=18.0,6.0 Hz, 1H), 2.94 (m, 3H), 2.76-2.65 (3H), 1.96 (m, 2H), 1.88 (d, J=11.0 Hz, 1H), 1.38 (t, J=7.0 Hz, 3H). This material was dissolved in excess 1N HCl MeOH and concentrated. Recrystallization from CH_2Cl_2/Et_2O provided a solid (74 mg, 68%). mp 243-245 °C.

EXAMPLE 14

5-ISOPROPOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol (208 mg, 0.75 mmol) and isopropyl alcohol (90 mg, 1.49 mmol) were converted to the title compound as described in Examples 12. (TLC of intermediate benzyl compound, 17%EtOAc/hexanes R_f 0.78). GCMS *m/e* 321 (M^+). Deprotection and conversion to the salt as described in Example 13 provided a solid (83 mg, 42% overall). (TLC of title compound, TLC 50%EtOAc/hexanes (NH_3) R_f 0.10). ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 6.89 (d, J=9.0 Hz, 1H), 6.66 (2H), 4.51 (m, 1H), 3.08 (dd, J=18.0,6.5 Hz, 1H), 2.98 (m, 3H), 2.78-2.68 (3H), 1.96 (m, 2H), 1.87 (d, J=11.0 Hz, 1H), 1.32 (t, J=5.5 Hz, 6H). mp 211-213 °C.

EXAMPLE 15

11-BENZYL-4-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 2-Cyclopent-3-enylmethyl-5-methoxy-phenol (For leading references, see: a) Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365-368; b) Lau, C. K.; Williams, H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Belanger, P, C. *Can. J. Chem.* **1989**, *67*, 1384-1387.)

3-Methoxyphenol (5.12 g, 42.0 mmol), cyclopent-3-enecarbaldehyde (8.00 g, 83.0 mmol), phenyl boronic acid (5.58 g, 46 mmol) and 1,1,1-trichloroacetic acid (2.04 g, 12.5 mmol) were refluxed in benzene (150 mL) for 18 hours. (TLC 5%CH_2Cl_2/hexanes R_f 0.47). The mixture was concentrated to an oil which was stirred at 0 °C in CH_2Cl_2 (100 mL) and treated with triethylsilane (8.87 g, 76.0 mmol) followed by trifluoroacetic acid (36.3 g, 318 mmol). The mixture was stirred for 1 hour then warmed to reflux for 24 hours. The mixture was concentrated, dissolved in CH_2Cl_2 (200 mL) and washed with a sat. aq. $NaHCO_3$ soln. (3 x 50 mL). The combined organic layer was dried through a cotton plug, concentrated and chromatographed on silica gel to provide an oil (3.85 g, 45%). (TLC 10%EtOAc/hexanes R_f 0.35). ^1H NMR ($CDCl_3$) δ 6.99 (d, J=8.0 Hz, 1H), 6.42 (dd, J=8.0,2.5 Hz, 1H), 6.36 (d, J=2.5 Hz, 1H), 5.67 (br s, 2H), 3.75 (s, 3H), 2.58 (m, 3H), 2.40 (m, 2H), 2.08 (m, 2H). GCMS *m/e* 204 (M^+).

B) Trifluoro-methanesulfonic acid 2-cyclopent-3-enylmethyl-5-methoxy-phenyl ester

2-Cyclopent-3-enylmethyl-5-methoxy-phenol (3.85 g, 19.0 mmol) was converted to the title compound (4.92 g, 77%) by the method described in Example 1D. (TLC 10%CH_2Cl_2/hexanes R_f 0.52). ^1H NMR ($CDCl_3$) δ 7.21 (d, J=8.0 Hz, 1H), 6.86 (dd, J=8.0,2.5 Hz, 1H), 6.79 (d, J=2.5 Hz, 1H), 5.67 (br s, 2H), 3.79 (s, 3H), 2.70 (d, J=7.5 Hz, 2H), 2.59 (m, 1H), 2.43 (m, 2H), 2.03 (m, 2H).

C) 4-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene

Trifluoro-methanesulfonic acid 2-cyclopent-3-enylmethyl-5-methoxy-phenyl ester (2.00 g, 5.95 mmol) was dissolved in DMF (10 mL) under a N_2 atmosphere and treated with triethylamine (0.91 g, 8.92 mmol) and 1,3-bis(diphenylphosphino)propane (0.37 g, 0.89 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles), and then treated with palladium acetate (93 mg, 0.42 mmol). After stirring for 20 min. the mixture was warmed to 100 °C for 18 hours, cooled and poured into brine (30 mL). The resulting mixture was extracted with EtOAc (4 x 10 mL) and the combined organic layer was washed with sat. aq. $NaHCO_3$ soln. (10 mL), H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated to an oil. The oil was chromatographed on Silica gel (2%CH_2Cl_2/hexanes) to provide product as an oil (1.05 g, 95%). (TLC 10%EtOAc/ hexanes R_f 0.52). ^1H NMR ($CDCl_3$) δ 6.94 (d, J=8.0 Hz, 1H), 6.68 (dd, J=8.0,2.8 Hz, 1H), 6.59 (d, J=2.8 Hz, 1H), 6.23 (dd, J=5.5,2.8 Hz,1H), 5.79 (dd, J=5.5,2.6 Hz, 1H), 3.77 (s, 3H), 3.28 (m, 1H), 2.96-2.89 (m, 2H), 2.49 (d, J=15.5 Hz, 1H), 2.19 (m, 1H), 1.85 (d, J=10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 156.94, 144.07, 138.95, 131.24, 131.21, 126.34, 111.73, 111.45, 55.22, 45.10, 40.18, 38.47, 29.49. GCMS *m/e* 186 (M^+).

D) 11-Benzyl-4-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

4-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (1.0 g, 5.37 mmol) was converted to 4-methoxy-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-triene (0.95 g, 80%) (TLC 50%EtOAc/CH_2Cl_2 R_f 0.46) according to the procedure described in Example 2G. This material was converted to the title compound according to the procedures described in Example 2H with final recrystallization from Et_2O/hexanes (650 mg, 46%). (TLC 50%EtOAc/CH_2Cl_2 R_f 0.67). ^1H NMR (CD_3OD) δ 7.42 (m, 5H), 7.12 (d, J=8.0 Hz, 1H), 6.84 (dd, J=8.0,2.5 Hz, 1H), 6.67 (d, J=2.5 Hz, 1H), 4.27 (AB d, J=13.0 Hz, 1H), 4.17 (AB d, J=13.0 Hz, 1H), 3.72 (s, 3H), 3.48 (br d , J=12.5 Hz, 1H), 3.34-3.16 (m, 5H), 2.86 (AB d, J=18.0 Hz, 1H), 2.55 (br s, 1H), 2.00 (AB d, J=13.0 Hz, 1H), 1.90 (AB d, J= 13.0 Hz, 1H). mp 245-246 °C.

EXAMPLE 16

4-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-4-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (525 mg, 1.60 mmol) was converted to the title compound by the methods described in Example 3 to provide a white solid (336 mg, 88%). (TLC 40%EtOAc/CH_2Cl_2 (NH_3) R_f 0.22). ^1H NMR (CD_3OD) δ 7.11 (d, J=8.5 Hz, 1H), 6.82 (dd, J=8.5,2.5 Hz, 1H), 6.75 (d, J=2.5 Hz, 1H), 3.76 (s, 3H), 3.34-3.16 (m, 6H), 2.86 (AB d, J=17.7Hz, 1H), 2.45 (m, 1H), 2.11 (AB d, J=13.5 Hz, 1H), 1.94 (AB d, J= 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 158.47, 136.58, 130.15, 127.71, 114.11, 112.61, 54.32, 49.99, 49.47, 32.16, 31.97, 27.15, 25.70. mp 259-261 °C.

EXAMPLE 17

11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-4-OL

4-Methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (120 mg, 0.50 mmol) was brought to reflux in 48%HBr (2 mL). After 1 hour the solution was cooled and poured into a 1N aq. NaOH soln. adjusted to pH 10 and product was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to a white solid which was recrystallized from Et_2O/hexanes (40 mg, 42%). (TLC 50%EtOAc/CH_2Cl_2 R_f 0.15). ^1H NMR ($CDCl_3$) δ 6.96 (d, J=8.0 Hz, 1H), 6.60 (dd, J=8.0,2.5 Hz, 1H), 6.46 (d, J=2.5 Hz, 1H), 3.31 (m, 1H), 3.03 (dd, J=17.0,6.0 Hz, 1H), 2.95 (m, 2H,NH), 2.73 (m, 3H), 1.99 (m, 2H), 1.87 (AB d, J= 12.5 Hz, 1H). mp 215-217 °C.

EXAMPLE 18

11-BENZYL-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared from phenol according to the procedures described in Example 15. (TLC 10%EtOAc/ hexanes (NH_3) R_f 0.76). ^1H NMR (CD_3OD) δ 7.42 (m, 5H), 7.22 (m, 2H), 7.15 (t, J=7.5 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 4.28 (AB d, J=13.0 Hz, 1H), 4.18

(AB d, J=13.0 Hz, 1H), 3.51 (d, J=12.8 Hz, 1H), 3.36 (d, J=13.2 Hz, 1H), 3.34-3.23 (m, 4H), 2.95 (d, J=12.2 Hz, 1H), 2.58 (m, 1H), 2.03 (AB d, J=13.0 Hz, 1H), 1.92 (AB d, J=13.0 Hz, 1H). mp 125-127 °C.

EXAMPLE 19

11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (150 mg, 0.50 mmol) was converted to the title compound as described in Example 3. (TLC 20%EtOAc/hexanes (NH_3) R_f 0.20). ^{1}H NMR (CD_3OD) δ 7.26-7.17 (m, 4H), 3.37-3.18 (m, 6H), 2.92 (d, J=16.2 Hz, 1H), 2.48 (m, 1H), 2.13 (AB d, J=13.0 Hz, 1H), 1.97 (AB d, J= 13.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 136.08, 135.67, 129.43, 128.78, 127.30, 126.42, 49.90, 49.05, 32.67, 31. 86, 27.15, 25.60. mp 227-228 °C.

EXAMPLE 20

4-NITRO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(11-Aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-2,2,2-trifluoro-ethanone

11-Aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene (1.22 g, 7.08 mmol) was stirred at 0 °C in CH_2Cl_2 (10 mL) and treated with triethylamine (0.94 mL, 10.6 mmol) followed by TFAA (1.90 mL, 14.2 mmol). After ~1 hour, the solution was poured into 0.5 N HCl (200 mL) and the layers separated. The aq. layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was washed with 0.5 N HCl (50 mL), H_2O (2 x 50 mL) and sat. aq. $NaHCO_3$ soln. (50 mL). This solution was dried through a cotton plug, then diluted with ~3% EtOAc and filtered through a 2 inch silica pad eluted with ~3% EtOAc/CH_2Cl_2. Concentration afforded a clear oil (1.90 g, 99%). ^{1}H NMR ($CDCl_3$) δ 7.15-7.02 (4H), 4.67 (d, J=13.0 Hz, 1/2H), 4.42 (d, J=13.0 Hz, 1/2H), 4.03 (d, J=13.0 Hz, 1/2H), 3.81 (d, J=13.0 Hz, 1/2H), 3.44 (d, J=13.0 Hz, 1H), 3.29-2.99 (3H), (d, J=18.0 Hz, 1H), 2.37 (br s, 1/2H), 2.30 (br s, 1/2H), 2.04 (AB d, 2H). GCMS *m/e* 269 (M^+).

B) ~Nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

The title compound was prepared as follows, based on the method described by Coon et al., *J. Org. Chem.*, **1973**, *25*, 4243. To a solution of trifluoromethanesulfonic acid (0.94 ml, 10.6 mmol) in CH_2Cl_2 (10 ml) stirred at 0 °C was slowly added nitric acid (0.60 ml, 14.1 mmol) generating a white precipitate. After 10 minutes the resulting mixture was cooled to -78 °C and treated with 1-(11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-2,2,2-trifluoro-ethanone (1.9 g, 7.06 mmol) in CH_2Cl_2 (15 ml) dropwise over 5 minutes. The reaction was stirred at -78 °C for 2h then warmed to 0 °C for 1/2 hour. The reaction mixture was poured into a stirred ice (50 g). The layers were separated and the aq. layer back extracted with CH_2Cl_2 (3 x 30 ml). The organic layer was combined and washed with H_2O (3

x 30 ml). The combined organic layer was washed with sat. aq. $NaHCO_3$ soln. (20 mL) and H_2O (20 mL) then dried through a cotton plug and concentrated to a yellow solid (1.58 g) which contained four products (TLC). The solids were slurried in Et_2O and filtered to provide a solid (900 mg, 41%). (TLC 30% EtOAc/hexanes, R_f 0.21). The filtrate was chromatographed on Silica gel eluting with 30% EtOAc/hexanes to provide three materials. R_f 0.32 (50 mg, 2%), R_f 0.21 (as solids above) and R_f 0.13 (50 mg, 2%). GCMS *m/e* 314 (M^+).

C) 4-Nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

NOE (Nuclear Overhauser Effect) experiments elucidated the primary product, (TLC 30%EtOAc/hexanes, R_f 0.21) as 2,2,2-trifluoro-1-(4-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-ethanone, by a 4% NOE between H-3 and H-1. This solid (780 mg, 2.48 mmol) was stirred in MeOH (20 mL) and treated with Na_2CO_3 (650 mg, 4.96 mmol) in H_2O (10 mL). The stirred mixture was warmed to 70°C for 6 hours, concentrated to solids, diluted with H_2O and extracted with CH_2Cl_2 (3 x 40 mL). The product was extracted into 1N aq. HCl soln. (3 x 40 mL) which was washed with EtOAc then neutralized with a sat. aq. Na_2CO_3 soln. to pH~10. Product was extracted with CH_2Cl_2 (3 x 40 mL), dried through a cotton plug, concentrated to an oil. The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) and concentrated, then dissolved in a minimum of CH_2Cl_2 and the solution was saturated with hexanes and stirred 18 hours. The product was collected by filtration (145 mg, 23%). ^{1}H NMR ($DMSO_{d-6}$) d 8.12 (d, J=2.5 Hz, 1H), 8.09 (d, J=8.0 Hz, 1H), 7.50 (dd, J=8.0,2.5 Hz, 1H), 3.25 (m, 3H), 3.08 (m, 3H), 2.88 (m, 2H), 2.27 (m,1H), 1.99 (d, J=11.0 Hz, 1H). GCMS *m/e* 218 (M^+). mp 215-220 °C.

EXAMPLE 21

5-NITRO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

The other meta substituted isomer from above, 2,2,2-trifluoro-1-(5-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-ethanone (TLC 30%EtOAc/hexanes, R_f 0.13) was converted to the title compound by the method in Example 20C. ^{1}H NMR free base ($CDCl_3$) δ 8.01 (d, J=2.0 Hz, 1H), 7.95 (dd, J=8.0,2.0 Hz, 1H), 7.17 (d, J=8.0 Hz, 1H), 3.16 (dd, J=18.0,6.5 Hz, 1H), 3.10-2.97 (4H), 2.89 (d, J=18.0 Hz, 1H), 2.79 (d, J=12.0 Hz, 1H), 2.12 (m, 1H), 2.02 (d, J=12.5 Hz, 1H), 1.88 (d, J=12.5 Hz, 1H). Conversion to the salt as in Example 20C provides a solid mp 245-255 °C.

EXAMPLE 22

3-NITRO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

The remaining isolated isomer from above, 2,2,2-trifluoro-1-(3-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-ethanone (TLC 30%EtOAc/hexanes, R_f 0.32) (50 mg) was converted to the title compound by the method in Example 20C to give 25 mg, 64%). The regiochemistry of this nitro isomer was established by HMQC (heteronuclear multiple-quantum correlation) between C-3 and H-1. ^{1}H NMR ($DMSO_{d-6}$) δ 7.80 (d, J=8.0 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 3.71-3.15 (m, 6H), 2.95 (d, J=18.5 Hz, 1H), 2.40 (br s, 1H), 2.04 (d, J=12.5 Hz, 1H), 1.70 (d, J=12.5 Hz, 1H).

EXAMPLE 23

11-BENZYL-5-FLUORO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared from 2-bromo-4-fluoro-1-methoxy-benzene by the methods described in Example 6. ^{1}H NMR (CD_3OD) δ 7.15 (m, 3H), 6.94-6.76 (m, 5H), 3.40 (AB d, 2H), 3.06 (dd, J=17.5,7.0 Hz, 1H), 2.87-2.73 (3H), 2.69 (d, J=10.5 Hz, 1H), 2.37 (d, J=10.5 Hz, 1H), 2.28 (d, J=10.5 Hz, 1H), 2.17 (br s, 1H), 1.83 (AB d, 2H). GCMS *m/e* 281 (M^+). mp 202-203 °C.

EXAMPLE 24

5-FLUORO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-5-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (310 mg, 0.94 mmol) was converted to the title compound by the methods described in Example 3 to yield a white solid (140 mg, 65%). ^{1}H NMR (CD_3OD) δ 7.22 (m, 1H), 6.93 (m, 2H), 3.38-3.14 (6H), 2.93 (d, J=18.5 Hz, 1H), 2.45 (m, 1H), 2.17 (AB d, J=13.0 Hz, 1H), 1.94 (AB d, J= 13.0 Hz, 1H). mp 286-287 °C.

EXAMPLE 25

5,7-DIOXA-14-AZATETRACYCLO[10.3.1.$0^{2,10}$.$0^{4,8}$]HEXADECA-2(10),3,8-TRIENE HYDROCHLORIDE

5-Bromo-6-methoxy-benzo[1,3]dioxole (Preparation described previously, see; Getahun, Z.; Jurd, L.; Chu, P. S.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1992**, *35*, 1058-1067.) was converted to the title compound using methods described in Example 3 and Example 6 to yield a white solid (110 mg). ^{1}H NMR (CD_3OD) δ 6.65 (s, 2H), 5.88 (s, 2H), 3.33-3.12 (6H), 2.81 (d, J=18.0 Hz, 1H), 2.42 (m, 1H), 2.09 (AB d, J=12.5 Hz, 1H), 1.90 (AB d, J= 12.5 Hz, 1H). GCMS *m/e* 217 (M^+). APCI MS *m/e* 218.1 [(M + 1)$^+$]. mp 241-243 °C.

EXAMPLE 26

11-BENZYL-6-BROMO-5-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5 -TRIENE

11-Benzyl-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5 -triene (3.00 g, 10.2 mmol) was stirred at 0°C in CH_2Cl_2 (10 mL) and AcOH (5 mL) and treated with bromine (3.21 g, 20 mmol) in CH_2Cl_2 (10 mL) and AcOH (5 mL). After 18 hours the reaction was quenched with 20% aq. $NaHSO_3$ soln. (100 mL). The product was extracted with CH_2Cl_2 (3 x 40 mL) and washed with sat. aq. $NaHCO_3$ soln. (3 x 50 mL). The combined organic layer was dried through a cotton plug, concentrated and chromatographed on Silica gel to provide an oil (1.05 g, 28%). (TLC 30%EtOAc/hexanes R_f 0.48). ^{1}H NMR ($CDCl_3$) δ 7.13 (m, 3H), 6.91 (m, 3H), 6.68 (d, J=8.0 Hz, 1H), 3.90 (s, 3H), 3.36 (s, 2H), 2.86-2.79 (4H), 2.67 (br d, J=9.0 Hz, 1H), 2.31 (br s, 1H), 2.28 (br s, 1H), 2.22 (br s, 1H), 1.78 (AB d, J=13.0 Hz, 2H). GCMS *m/e* 373,371 (M^+).

EXAMPLE 27

11-BENZYL-6-HYDROXY-5-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5 -TRIENE

11-Benzyl-6-bromo-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5 -triene (1.05 g, 2.70 mmol) was stirred at -78 °C in anh. THF (10 mL) and treated with n-BuLi (1.08 mL. 2.5M soln. in hexanes, 2.70 mmol) dropwise over 1 min. After 10 min., triisopropyl borate (559 mg, 2.97 mmol) was added and the mixture was allowed to warm to ambient temperature. The reaction was quenched with with sat. aq. $NaHCO_3$ soln. (50 mL) and the product was extracted with EtOAc (3 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give an oil (640 mg, 67%). (TLC 30%EtOAc/hexanes R_f 0.18). This material (640 mg, 1.81 mmol) was stirred in THF (10 mL) with 30% aq. hydrogen peroxide soln. (205 mg, 1.81 mmol). After 18 hours the reaction was quenched with 20% aq. $NaHSO_3$ soln. (10 mL). The mixture was diluted with sat. aq. $NaHCO_3$ soln. (50 mL) and product was extracted with CH_2Cl_2 (3 x 40 mL). The organic layer washed with sat. aq. $NaHCO_3$ soln. (3 x 50 mL), dried through a cotton plug, concentrated and chromatographed on Silica gel to provide an oil (360 mg, 64%). (TLC 40%EtOAc/hexanes R_f 0.44). ^{1}H NMR ($CDCl_3$) δ 7.14 (3H), 6.95 (2H), 6.67 (d, J=8.0 Hz, 1H), 6.52 (d, J=8.0 Hz, 1H), 3.89 (s, 3H), 3.40 (AB d, 2H), 2.88-2.63 (5H), 2.34-2.22 (3H), 1.79 (AB d, 2H). GCMS *m/e* 309 (M^+).

EXAMPLE 28

6-HYDROXY-5-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5 -TRIENE HYDROCHLORIDE

11-Benzyl-6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5 -triene (58 mg, 0.18 mmol) was converted to the title compound according to the procedure described in

Example 3 followed by conversion to the salt as described in Example 9 to provide a white solid (15 mg, 32%). (TLC 10%MeOH/CH_2Cl_2 (NH_3) R_f 0.26). ^1H NMR (CD_3OD) δ 6.84 (d, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 3.82 (s, 3H), 3.29 (3H), 3.13 (m, 2H), 3.00 (dd, J=18.0,6.0 Hz, 1H), 2.85 (d, J=18.0 Hz, 1H), 2.42 (m, 1H), 2.09 (AB d, J=12.5 Hz, 1H), 1.82 (AB d, J= 12.5 Hz, 1H). mp 285-290 °C.

EXAMPLE 29

TRIFLUORO-METHANESULFONIC ACID-11-BENZYL-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-5-YL ESTER

11-Benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol (850 mg, 3.03 mmol) was converted to the title compound (1.18 g, 94%) by the method described in Example 1D. (TLC 30%EtOAc/hexanes R_f 0.47). ^1H NMR ($CDCl_3$) δ 7.10 (3H), 6.97 (3H), 6.78 (2H), 3.40 (AB d, J=14.0 Hz, 1H), 3.30 (AB d, J=14.0 Hz, 1H), 3.05 (AB dd, J=17.5,7.0 Hz, 1H), 2.89-2.79 (3H), 2.62 (d, J=10.0 Hz, 1H), 2.40 (d, J=10.5 Hz, 1H), 2.28 (d, J=12.0 Hz, 1H), 2.17 (br s, 1H), 1.83 (AB d, 2H). APCI MS *m/e* 412.1 [$(M + 1)^+$].

EXAMPLE 30

5-(4-TRIFLUOROMETHYL-PHENYL)-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 11-Benzyl-5-(4-trifluoromethyl-phenyl)-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene (For a discussion, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.)

Trifluoro-methanesulfonic acid-11-benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl ester (258 mg, 0.63 mmol), potassium acetate (493 mg, 5.02 mmol) and 4-trifluoromethylphenyl boronic acid (141 mg, 0.94 mmol) were combined in 10/1 EtOH/H_2O (5 mL). The mixture was degassed (3 vacuum/N_2 cycles), treated with tetrakis(triphenylphosphine)palladium(0) (36.0 mg, 0.032 mmol) and warmed to 90 °C for 18h. The reaction was cooled, diluted with H_2O and extracted with Et_2O (3 x 50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to provide an oil (60 mg, 23%). (TLC hexanes R_f 0.16). ^1H NMR ($CDCl_3$) δ 7.73 (d, J=8.5 Hz, 2H), 7.68 (d, J=8.5 Hz, 2H), 7.38 (d, J=2.0 Hz, 1H), 7.32 (dd, J=8.0,2.0 Hz, 1H), 7.10 (4H), 6.88 (m, 2H), 3.40 (s, 2H), 3.14 (dd, J= 17.5, 7.0 Hz, 1H), 2.94-2.87 (3H), 2.76 (d, J=10.5 Hz, 1H), 2.40 (dd, J=10.5,2.0 Hz, 1H), 2.33 (dd, J=10.5,2.0 Hz, 1H), 2.22 (br s, 1H), 1.91 (AB d, J=12.5 Hz, 1H), 1.83 (AB d, J=12.5 Hz, 1H). GCMS *m/e* 407 $(M)^+$.

B) 5-(4-Trifluoromethyl-phenyl)-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

11-Benzyl-5-(4-Trifluoromethyl-phenyl)-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene was converted to the title compound as described in Example 3. (TLC

50%EtOAc/hexanes R_f 0.81). ^1H NMR ($CDCl_3$) δ 7.62 (m, 4H), 7.15-6.98 (3H) 3.50-2.97 (6H), 2.92 (d, J=18.0 Hz, 1H), 2.38 (br s, 1H), 2.02 (AB d, 2H).

EXAMPLE 31

5-(4-METHOXY-PHENYL)-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

Trifluoro-methanesulfonic acid-11-benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl ester and 4-methoxyphenyl boronic acid were converted to the title compound by the methods described in Example 30. ^1H NMR (CD_3OD) δ 7.57 (d, J=8.0 Hz, 2H), 7.42 (d, J=2.0 Hz, 1H), 7.38 (dd, J=8.0,2.0 Hz, 1H), 7.18 (d, J=8.0 Hz, 1H), 6.97 (d, J=8.0 Hz, 2H), 3.81 (s, 3H), 3.48-3.08 (6H), 2.95 (d, J=18.0 Hz, 1H), 2.30 (br s, 1H), 2.10 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H).

EXAMPLE 32

11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE-5-CARBOXYLIC ACID METHYL ESTER HYDROCHLORIDE (Based on Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904-905.)

Trifluoro-methanesulfonic acid-11-benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl ester (1.0 g, 2.26 mmol) was dissolved in DMSO (15 mL) and MeOH (2 mL) and treated with triethylamine (505 mg, 4.99 mmol), potassium acetate (22.0 mg, 0.23 mmol) and 1,3-bis(diphenylphosphino)propane (94.0 mg, 0.23 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles) then treated with palladium acetate (51 mg, 0.23 mmol). The system was purged with carbon monoxide gas (CO(g)) at balloon pressure, stirred 20 min., warmed to 100°C for 3 hours, cooled and then poured into brine (50 mL). The resulting mixture was extracted with EtOAc (4 x 40 mL) and the combined organic layer was washed with a sat. aq. $NaHCO_3$ soln. (100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and evaporated to an oil. The oil, 11-benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5-carboxylic acid methyl ester, was chromatographed on silica gel to provide an oil (280 mg, 38%). (TLC 10%EtOAc/ hexanes R_f 0.21). APCI MS *m/e* 322.2 [(M + 1)$^+$]. This oil was converted into the title compound by the methods described in Example 3. (TLC 10%CH_2Cl_2/MeOH (NH_3) R_f 0.21). ^1H NMR (CD_3OD) δ 7.87 (d, J=2.0 Hz, 1H), 7.83 (dd, J=8.0,2.0 Hz,1H), 7.35 (d, J=8.0 Hz, 1H), 3.87 (s, 3H), 3.49-3.12 (6H), 2.97 (d, J=18.5 Hz, 1H), 2.52 (br s, 1H), 2.18 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H). mp 255-256 °C.

EXAMPLE 33

2-(11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIEN-5-YL)-PROPAN-2-OL HYDROCHLORIDE

11-Benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5-carboxylic acid methyl ester (180 mg, 0.62 mmol) was stirred under N_2 at -78 °C in anh. THF (15 mL) and treated with excess methyl magnesiumbromide (~1 mL, 3M in THF). The resulting mixture was allowed to warm to ambient temperature and quenched with a sat. aq. NH_4Cl soln. (25 mL). The product was extracted with EtOAc (3 x 50 mL), washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated to an oil (100 mg, 50%). GCMS *m/e* 321 (M^+). This material was converted to the title compound by the methods described in Example 3. ^1H NMR (CD_3OD) δ 7.32 (OH), 7.24 (s, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.08 (m, 1H), 3.50-3.12 (6H), 2.91 (d, J=18.5 Hz, 1H), 2.47 (br, s, 1H), 2.11 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H), 1.15 (s, 6H). mp 80-81°C.

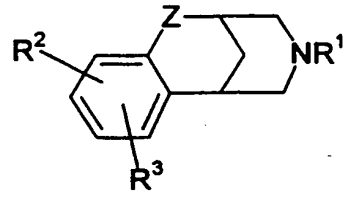
EXAMPLE 34

5-Pyridin-3-yl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene hydrochloride

Trifluoro-methanesulfonic acid 11-benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl ester and diethyl-pyridin-3-yl-borane were converted to the title compound by the methods described in Example 30. ^1H NMR (CD_3OD) δ 9.14 (br s, 1H), 8.78 (m, 2H), 8.08 (m, 1H), 7.69 (d, J=2.0 Hz, 1H), 7.62 (dd, J=8.0,2.0 Hz,1H), 7.43 (d, J=8.0 Hz, 1H), 3.43-3.18 (6H), 3.05 (d, J=18.5 Hz, 1H), 2.56 (br s, 1H), 2.18 (AB d, J=11.5 Hz, 1H), 2.02 (AB d, J=11.5 Hz, 1H). GCMS *m/e* 250 (M^+). mp 240-242 °C.

CLAIMS

1. A compound of the formula



(I)

wherein Z is CH_2, C(=O) or CF_2;

R^1 is hydrogen, $(C_1$-$C_6)$alkyl, unconjugated $(C_3$-$C_6)$alkenyl, benzyl, $XC(=O)R^{13}$ or $-CH_2CH_2$-O-$(C_1$-$C_4)$alkyl;

R^2 and R^3 are selected independently, from hydrogen, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, hydroxy, nitro, amino, halo, cyano, $-SO_q(C_1$-$C_6)$alkyl wherein q is zero, one or two, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$amino, CO_2R^4, $CONR^5R^6$, $SO_2NR^7R^8$, $C(=O)R^{13}$, $XC(=O)R^{13}$, aryl-$(C_0$-$C_3)$ alkyl or aryl-$(C_0$-$C_3)$alkyl-O- wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0$-$C_3)$alkyl or heteroaryl-$(C_0$-$C_3)$alkyl-O-, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and $X^2(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl, wherein X^2 is absent or X^2 is $(C_1$-$C_6)$alkylamino or $[(C_1$-$C_6)$alkyl$]_2$amino, and wherein the $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl moiety of said $X^2(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl may be optionally substituted with from two to seven fluorine atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-$(C_0$-$C_3)$alkyl and said heteroaryl-$(C_0$-$C_3)$alkyl may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1$-$C_6)$ alkyl optionally substituted with from one to seven fluorine atoms, $(C_1$-$C_6)$ alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), hydroxy, nitro, cyano, amino, $(C_1$-$C_6)$ alkylamino and $[(C_1$-$C_6)$ alkyl$]_2$ amino;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with

one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from (C_0-C_6) alkoxy-(C_0-C_6)alkyl-, wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, oxo, cyano, halo, hydroxy, amino, (C_1 -C_6)alkylamino, [(C_1 -C_6) alkyl]$_2$amino, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as in the definition of R^2 and R^3 above;

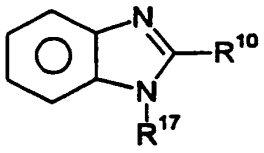
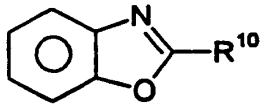
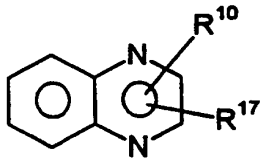
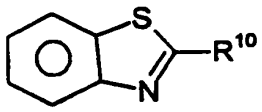
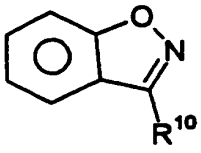
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, -N-(C_1-C_6)alkylpiperizine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1-C_6)alkylene;

with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen; and (c) no fluorine atom in any of the fluoro substituted alkyl or alkoxy moieties of R^2 and R^3 can be attached to a carbon that is attached to a heteroatom;

or a pharmaceutically acceptable salt thereof;

2. A compound according to claim 1, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:

wherein R^{10} and R^{17} are selected, independently, from hydrogen and (C_1-C_6)alkyl.

3. A compound according to claim 1, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

4. A compound according to claim 1, wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$ wherein R^{13} is (C_1-C_6)alkyl.

5. A compound according to claim 1, wherein one of R^2 and R^3 is $-COR^{13}$ wherein R^{13} is (C_1-C_6)alkyl or (C_1-C_3)alkyl optionally substituted with from one to seven fluorine atoms.

6. A compound according to claim 1, wherein one of R^2 and R^3 is CF_3 , fluoro, cyano or C_2F_5.

7. A pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

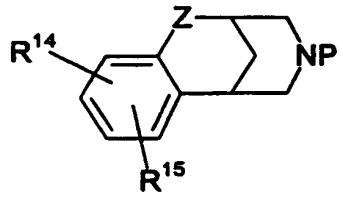
8. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

9. A pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, headache, stroke, TBI, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

10. A method for treating a disorder or condition selected from inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, headache, stroke, TBI, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering

to a mammal in need of such treatment an amount of a compound according to claim 1 that is effective in treating such disorder or condition.

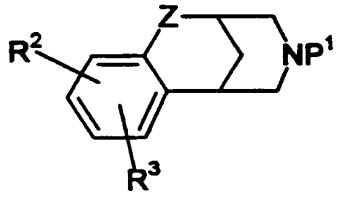
11. A compound of the formula



(I)

wherein Z is CH_2, CF_3 or C(=O); P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1$-$C_6)$alkyl, allyl or 2,2,2-trichloroethyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, $-C(=O)(C_1$-$C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl or t-butoxycarbonyl (t-Boc), and R^{14} and R^{15} are selected, independently, from hydroxy, nitro, amino, $-O(C_1$-$C_6)$alkyl and halo; with the proviso that R^{14} and R^{15} cannot both be hydrogen when P is hydrogen or methyl.

12. A compound of the formula



(I)

wherein Z is CH_2, CF_3 or C(=O); R^2 and R^3 are defined as in claim 2; and P^1 is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or $(C_1$-$C_6)$alkyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, $-C(=O)(C_1$-$C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl, t-butoxycarbonyl (t-Boc), or trifluoroacetyl.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/IB 99/00617

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/22 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WEI K. CHANG ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 14, no. 10, 1971, pages 1011-3, XP002108896 see table I, compounds no. 1-4 ---	1,3,11
A	K. KITAHONOKI ET AL.: TETRAHEDRON, vol. 25, no. 2, 1969, pages 335-53, XP002108897 see page 341, compound XXXVa ---	1,3,11
A	T. KOMETANI ET AL.: CHEM. PHARM. BULL., vol. 24, no. 3, 1976, pages 541-4, XP002108898 see page 542, chart 2, compounds X and XIb --- -/--	1,3,11

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 1999	29/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter .nal Application No
PCT/IB 99/00617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropnate, of the relevant passages	Relevant to claim No.
A	K. KITAHONOKI ET AL.: TETRAHEDRON LETTERS, no. 13, 1968, pages 1651-5, XP002108899 see page 1652, compound Xa	1,3,11
A	CHEMICAL ABSTRACTS, vol. 81, no. 13, 30 September 1974 (1974-09-30) Columbus, Ohio, US; abstract no. 77812w, page 452; XP002108900 & JP 49 024968 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 5 March 1974 (1974-03-05)	1,3,9,11
A	CHEMICAL ABSTRACTS, vol. 80, no. 19, 13 May 1974 (1974-05-13) Columbus, Ohio, US; abstract no. 108399c, page 407; XP002108901 & JP 49 014473 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 7 February 1974 (1974-02-07)	1,3,9,11

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/00617

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IB 99 /00617

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

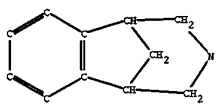
Although claims 8 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

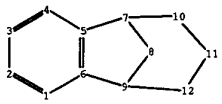
Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Feb. 7, 2002

C:\STNEXP4\QUERIES\09402010.str

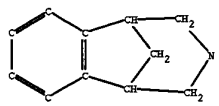


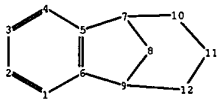


ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-9 7-8 7-10 8-9 9-12 10-11 11-12
exact/norm bonds :
5-7 6-9 7-8 7-10 8-9 9-12 10-11 11-12
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom

C:\STNEXP4\QUERIES\09402010a.str





ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-9 7-8 7-10 8-9 9-12 10-11
11-12
exact bonds :
5-7 6-9 7-8 7-10 8-9 9-12 10-11 11-12
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6
isolated ring systems :
containing 1 :

not
out

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom
10:Atom 11:Atom 12:Atom

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=> d his

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     FILE 'REGISTRY' ENTERED AT 18:39:25 ON 07 FEB 2002
L1             SCREEN 1841
L2             STRUCTURE UPLOADED
L3             QUE L2 AND L1
L4           3 S L3
L5             STRUCTURE UPLOADED
L6             QUE L5
L7          10 S L6
L8       36551 S C5/ESS(S)NC5/ESS(S)C6/ESS
L9           3 S L3  SUB=L4 SAM
L10          3 S L3  SUB=L4 FUL

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L11          1 S WO9935131/PN
               SELECT RN L11 1

     FILE 'REGISTRY' ENTERED AT 18:50:03 ON 07 FEB 2002
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L13        172 S 1332.25/RID
L14         60 S L12 AND L13
L15         63 S L12 NOT L14
L16         35 S L8 AND L15
L17         11 S L3  SUB=L8 SAM
L18        205 S L3  SUB=L8 FUL
L19         10 S L6  SUB=L8 SAM
L20        165 S L6  SUB=L8 FUL
L21        173 S L18 NOT L20

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L23          8 S L22 AND PATENT/DT

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L2             STR
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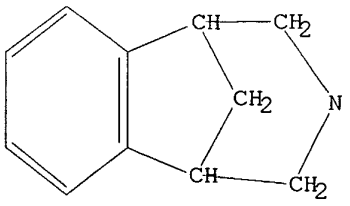


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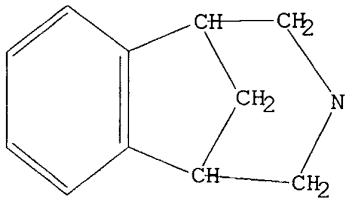
L5 STR



Structure attributes must be viewed using STN Express query preparation.
L6 QUE ABB=ON PLU=ON L5

=> d bib abs hitstr l23 1-8

L23 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 2001:885334 CAPLUS
DN 136:658
TI A pharmaceutical composition for the treatment of obesity or to facilitate or promote weight loss, comprising a nicotine receptor partial agonist and an anti-obesity agent
IN Coe, Jotham W.; O'Neill, Brian T.; Sands, Steven B.; Dow, Robert L. B.; Harrigan, Edmund P.; Watsky, Eric J.
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1159970	A2	20011205	EP 2001-304806	20010531
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 2002010192	A1	20020124	US 2001-850042	20010507
	JP 2002012558	A2	20020115	JP 2001-164010	20010531
PRAI	US 2000-208856	P	20000602		

AB Pharmaceutical compns. are disclosed for the treatment of obesity, an overweight condition and compulsive overeating. The pharmaceutical compns. are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an anti-obesity agent or wt. loss facilitator or promoter, such as Xenical and Meridia, and a pharmaceutically acceptable carrier. The nicotine receptor partial agonist and an anti-obesity agent or wt. loss facilitator are administered substantially simultaneously. A method of treating a disorder or condition in which obesity or an overweight condition predominates, including type 2 diabetes mellitus, hypertension, dislipidemia, and increased mortality in a mammal comprises administering a compn. contg. nicotine receptor partial agonist and an anti-obesity agent.

IT **230615-75-5 249296-44-4 328055-77-2**
328055-78-3 328055-79-4 328055-83-0
328055-87-4 328055-88-5 328055-89-6
328055-90-9 328055-92-1 328055-98-7
357424-19-2 357424-20-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising nicotine receptor partial agonist and antiobesity agent for treatment of obesity and related disorders)

RN 230615-75-5 CAPLUS
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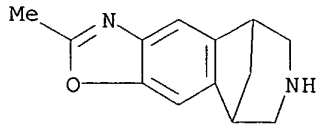

RN 249296-44-4 CAPLUS
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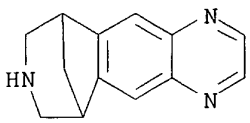
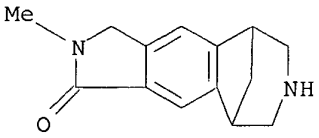
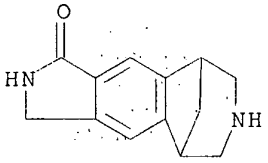


RN 328055-77-2 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



RN 328055-78-3 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



RN 328055-79-4 CAPLUS
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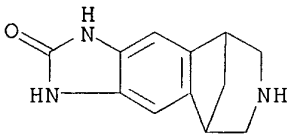

RN 328055-83-0 CAPLUS
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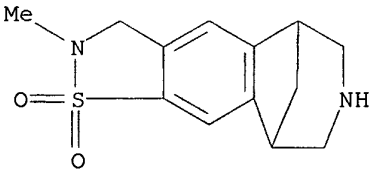

RN 328055-87-4 CAPLUS
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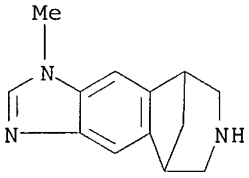

RN 328055-88-5 CAPLUS
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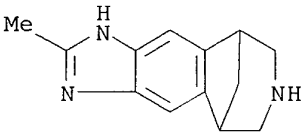
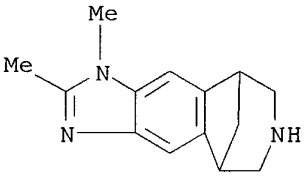
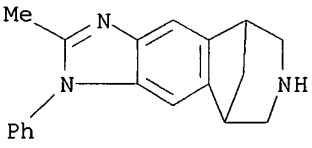


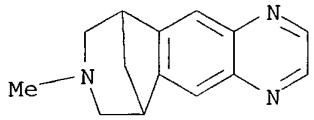
RN 328055-89-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl- (9CI) (CA INDEX NAME)



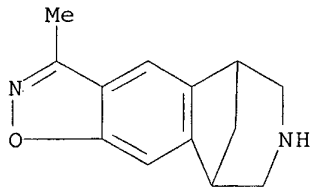
RN 328055-90-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl- (9CI) (CA INDEX NAME)



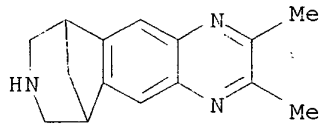
RN 328055-92-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl- (9CI) (CA INDEX NAME)



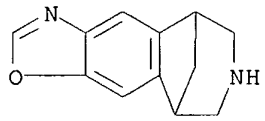
RN 328055-98-7 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl- (9CI) (CA INDEX NAME)



RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



RN 357424-20-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro- (9CI) (CA INDEX NAME)

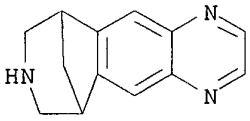


L23 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 2001:864711 CAPLUS
DN 136:11124
TI Reactive crystallization method to improve particle size
IN Am Ende, David Jon; Crawford, Thomas Charles; Weston, Neil Philip
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1157726	A1	20011128	EP 2001-304422	20010518
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002028475	A2	20020129	JP 2001-153592	20010523
	CN 1326803	A	20011219	CN 2001-119055	20010525
PRAI	US 2000-207629	P	20000526		

AB This invention provides a method of conducting a simultaneous chem. reaction and controlled crystn. of the product employing impinging fluid jet streams contg. reactants capable of producing the product with desired particle size characteristics. An example is give for reaction and crystn. of ziprasidone to achieve the desired ziprasidone-HCl.H2O.

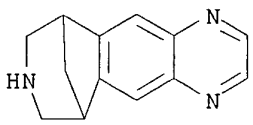
IT **249296-44-4**
RL: PRP (Properties); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(reactive crystn. method to improve particle size)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



IT **375815-87-5P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reactive crystn. method to improve particle size)
RN 375815-87-5 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

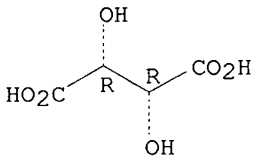
CRN 249296-44-4
CMF C13 H13 N3



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 2001:798758 CAPLUS
DN 135:339282
TI Nicotine receptor partial agonist, cholinesterase inhibitor, and estrogenic agent composition for treatment of diseases of cognitive dysfunction in a mammal
IN Coe, Jotham Wadsworth; Sands, Steven Bradley; Harrigan, Edmund Patrick; O'Neill, Brian Thomas; Watsky, Eric Jacob
PA USA
SO U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001036949	A1	20011101	US 2001-760966	20010116
WO 2001085145	A2	20011115	WO 2001-IB681	20010424

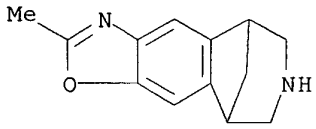
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-202799 P 20000509

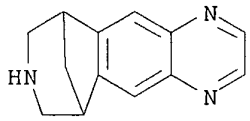
AB A pharmaceutical compn. and method of treatment of diseases of cognitive dysfunction in a mammal comprising administration of a nicotine receptor partial agonist or a pharmaceutically acceptable salt thereof; and an acetylcholinesterase inhibitor, butylcholinesterase inhibitor, an estrogenic agent, selective estrogen receptor modulator or muscarinic agonist or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. The nicotine receptor partial agonist and acetylcholinesterase inhibitor, butylcholinesterase inhibitor, estrogen, selective estrogen receptor modulator or muscarinic agonist are present in amts. that render the compn. effective enhancing cognition or in the treatment of diseases of cognitive dysfunction including but not limited to Alzheimer's Disease, mild cognitive impairment, age-related cognitive decline, vascular dementia, Parkinson's disease dementia, Huntington's Disease, Stroke, TBI, AIDS assocd. dementia and schizophrenia. The method of using these compns. is also disclosed.

IT **230615-75-5 249296-44-4 328055-77-2**
328055-78-3 328055-79-4 328055-83-0
328055-87-4 328055-88-5 328055-89-6
328055-90-9 328055-92-1 328055-98-7
357424-19-2 357424-20-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nicotine receptor partial agonist, cholinesterase inhibitor, and estrogenic agent compn. for treatment of diseases of cognitive dysfunction in a mammal)

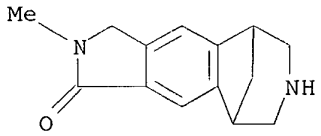
RN 230615-75-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



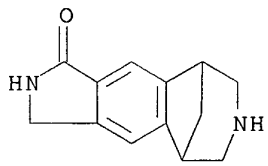
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



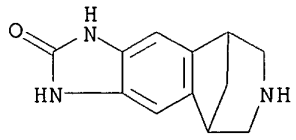
RN 328055-77-2 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



RN 328055-78-3 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)

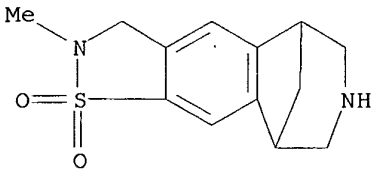


RN 328055-79-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)

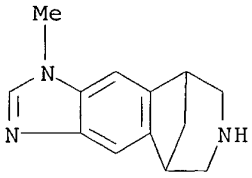


RN 328055-83-0 CAPLUS

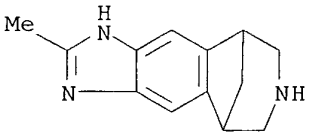
CN 5,9-Methano-2H-isothiazolo[4,5-h][3]benzazepine, 3,5,6,7,8,9-hexahydro-2-methyl-, 1,1-dioxide (9CI) (CA INDEX NAME)



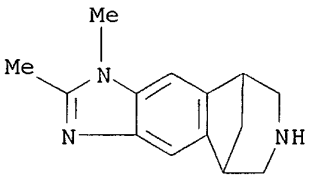
RN 328055-87-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl- (9CI) (CA INDEX NAME)



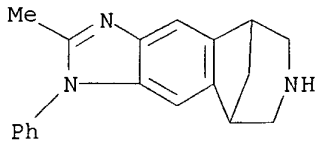
RN 328055-88-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



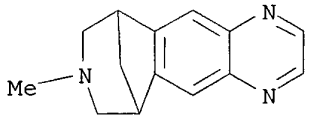
RN 328055-89-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl- (9CI) (CA INDEX NAME)



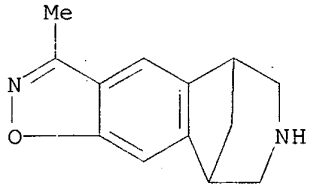
RN 328055-90-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl- (9CI) (CA INDEX NAME)



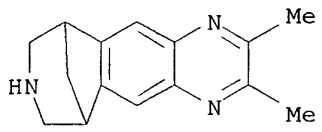
RN 328055-92-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl- (9CI) (CA INDEX NAME)



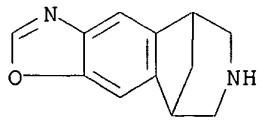
RN 328055-98-7 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl- (9CI) (CA INDEX NAME)



RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



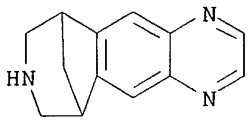
RN 357424-20-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro- (9CI) (CA INDEX NAME)



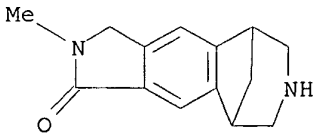
L23 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 2001:762800 CAPLUS
DN 135:322726
TI A pharmaceutical composition containing a nicotine receptor agonist and an analgesic for treatment of acute, chronic pain and/or neuropathic pain and migraines
IN Coe, Jotham Wadsworth; Harrigan, Edmund Patrick; O'Neill, Brian Thomas; Sands, Steven Bradley; Watsky, Eric Jacob
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001076576	A2	20011018	WO 2001-IB391	20010316
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2001036943	A1	20011101	US 2000-740307	20001218
PRAI	US 2000-195738	P	20000407		

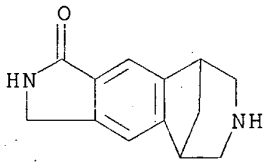
AB Oral, parenteral or transdermal compns. are disclosed for the treatment of acute, chronic and/or neuropathic pain. The pharmaceutical compns. are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an analgesic agent and a pharmaceutically acceptable carrier. The analgesic agent is selected from opioid analgesics, NMDA antagonists, substance P antagonists, COX 1 and COX 2 inhibitors, tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), capsaicin receptor agonists, anesthetic agents, benzodiazepines, skeletal muscle relaxants, migraine therapeutic agents, anticonvulsants, antihypertensives, antiarrhythmics, antihistamines, steroids, caffeine, N-type calcium channel antagonists and botulinum toxin. The method of using these compds. and a method of treating acute, chronic and/or neuropathic pain and migraine in a mammal including a human is also disclosed.
IT **249296-44-4 328055-77-2 328055-78-3**
328055-79-4 328055-83-0 328055-87-4
328055-88-5 328055-89-6 328055-90-9
328055-92-1 357424-19-2 367511-27-1
367511-30-6 367511-38-4
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. contg. nicotine receptor agonist and analgesic for treatment of acute, chronic pain and/or neuropathic pain and migraines)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



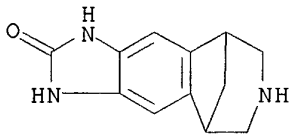
RN 328055-77-2 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



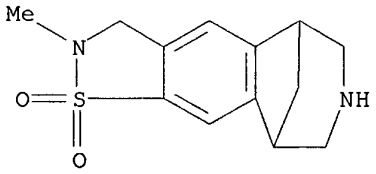
RN 328055-78-3 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



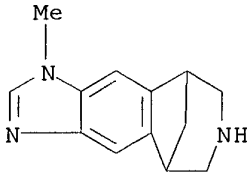
RN 328055-79-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



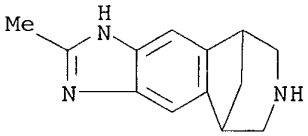
RN 328055-83-0 CAPLUS
CN 5,9-Methano-2H-isothiazolo[4,5-h][3]benzazepine, 3,5,6,7,8,9-hexahydro-2-methyl-, 1,1-dioxide (9CI) (CA INDEX NAME)



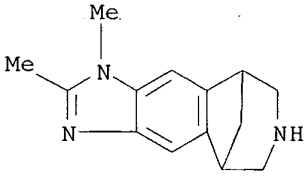
RN 328055-87-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl- (9CI) (CA INDEX NAME)



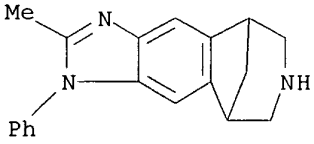
RN 328055-88-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



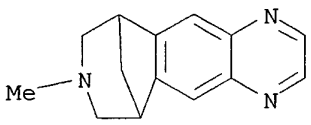
RN 328055-89-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl- (9CI) (CA INDEX NAME)



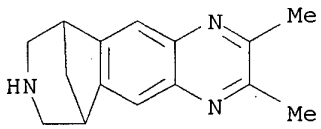
RN 328055-90-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl- (9CI) (CA INDEX NAME)



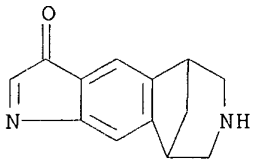
RN 328055-92-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl- (9CI) (CA INDEX NAME)



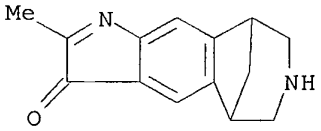
RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



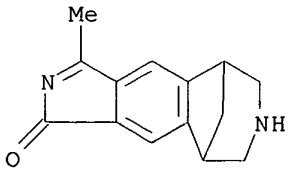
RN 367511-27-1 CAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-3(5H)-one, 6,7,8,9-tetrahydro- (9CI) (CA INDEX NAME)



RN 367511-30-6 CAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-3(5H)-one, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



RN 367511-38-4 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(5H)-one, 6,7,8,9-tetrahydro-3-methyl- (9CI) (CA INDEX NAME)



L23 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 2001:636053 CAPLUS
DN 135:210949
TI Preparation of aryl-fused azapolycyclic compounds as nicotine binding inhibitors
IN Brooks, Paige Roanne Palmer; Coe, Jotham Wadsworth
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062736	A1	20010830	WO 2001-IB153	20010208

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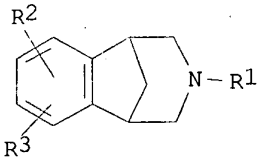
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-514002 A 20000225
OS MARPAT 135:210949
GI

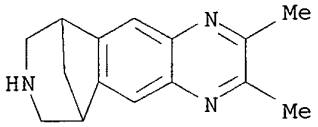


I

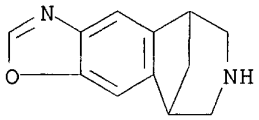
AB The invention discloses the prepn. of aryl-fused azapolycyclic compds., such as I [R1 = H, alkyl, unconjugated alkenyl, benzyl, X(CO)R13, CH2CH2O-alkyl; R2, R3 = H, alkenyl, alkynyl, hydroxy, nitro, amino, halo, cyano, SOqalkyl, (q = 0 - 2), alkylamino, CO2R4, CONR5R6, SO2NR7R8, COR13, X(CO)R13; R2 and R3, together with the carbons to which they are attached form a 4-7 membered monocyclic ring or a 10-14 membered bicyclic ring; R4-R8, R13 = H, alkyl or R5 and R6, or R7 and R8 together with nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, thiomorpholine; X = alkylene], and their pharmaceutically acceptable salts, as nicotine binding inhibitors (IC50 < 10 .mu.M) in the treatment of neurol. and psychol. disorders. Thus, aryl-fused azapolycyclic compd. I (R1-R3 = H) was prepd. via a multistep synthetic sequence starting from 2-fluorobromobenzene via a cycloaddn. with cyclopentadiene and an amination with triethylbenzylammonium chloride.

IT **357424-19-2P 357424-20-5P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryl-fused azapolycyclic compds. as nicotine binding

inhibitors)
RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



RN 357424-20-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro- (9CI) (CA INDEX NAME)



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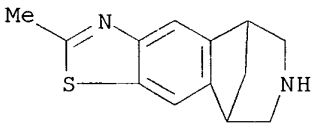
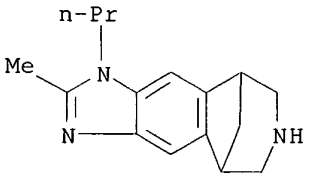
357425-88-8P 357425-89-9P 357425-90-2P
357425-91-3P 357425-92-4P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryl-fused azapolycyclic compds. as nicotine binding inhibitors)

RN 230615-07-3 CAPLUS
CN 5,9-Methano-5H-thiazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



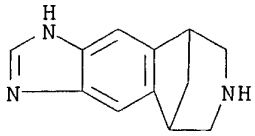
● HCl

RN 230615-09-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-propyl-, monohydrochloride (9CI) (CA INDEX NAME)



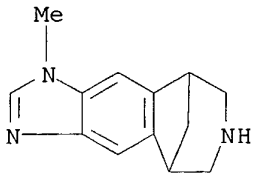
● HCl

RN 230615-10-8 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



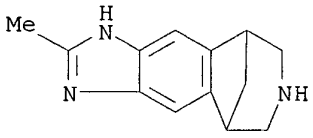
● HCl

RN 230615-11-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



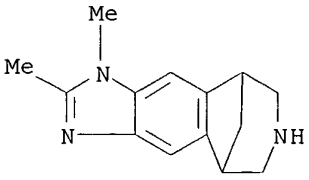
● HCl

RN 230615-12-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



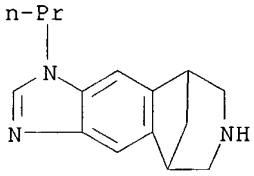
● HCl

RN 230615-13-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



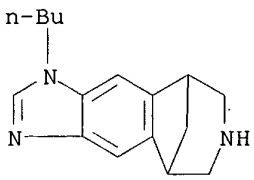
● HCl

RN 230615-14-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-propyl-, monohydrochloride (9CI) (CA INDEX NAME)



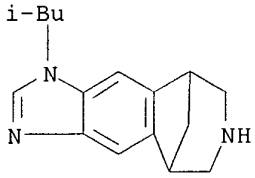
● HCl

RN 230615-15-3 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-butyl-1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



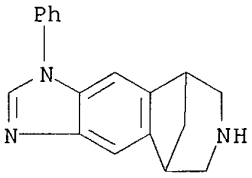
● HCl

RN 230615-16-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-(2-methylpropyl)-, monohydrochloride (9CI) (CA INDEX NAME)



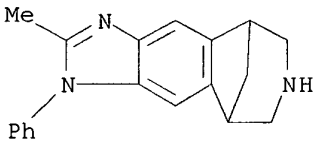
● HCl

RN 230615-17-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)



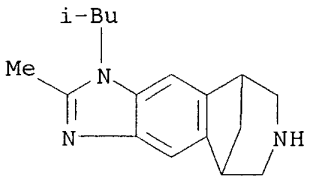
● HCl

RN 230615-18-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)



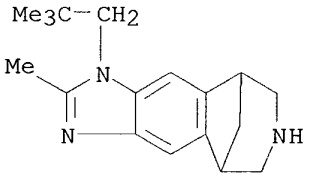
● HCl

RN 230615-19-7 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-(2-methylpropyl)-, monohydrochloride (9CI) (CA INDEX NAME)



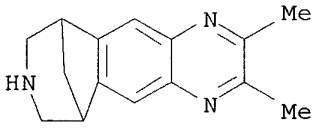
● HCl

RN 230615-20-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



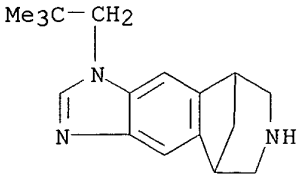
● HCl

RN 230615-21-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



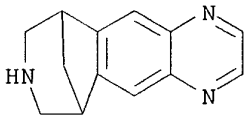
● HCl

RN 230615-22-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



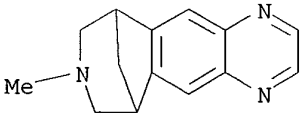
● HCl

RN 230615-23-3 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



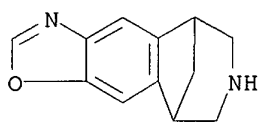
● HCl

RN 230615-24-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



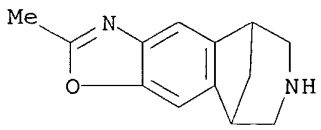
● HCl

RN 230615-25-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



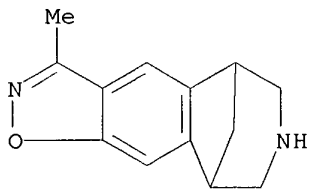
● HCl

RN 230615-26-6 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



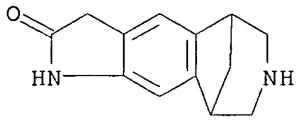
● HCl

RN 230615-33-5 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



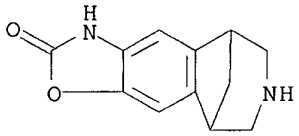
● HCl

RN 230615-39-1 CAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



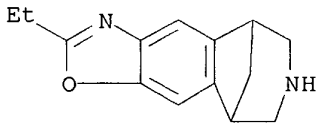
● HCl

RN 230615-40-4 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



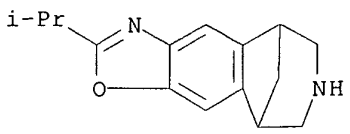
● HCl

RN 230615-44-8 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 2-ethyl-6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



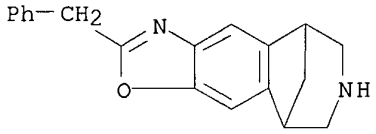
● HCl

RN 230615-45-9 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-(1-methylethyl)-, monohydrochloride (9CI) (CA INDEX NAME)



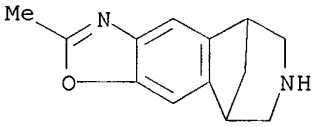
● HCl

RN 230615-46-0 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

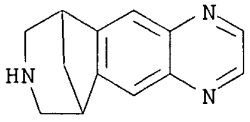


● HCl

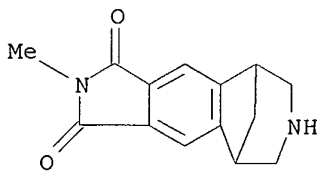
RN 230615-75-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



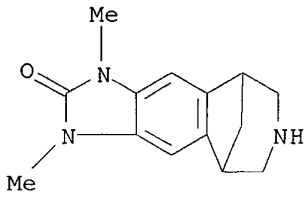
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



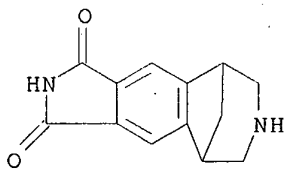
RN 287973-24-4 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepine-1,3(2H,5H)-dione, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



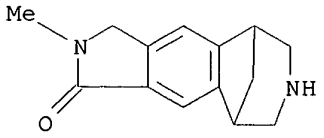
RN 287973-25-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-1,3-dimethyl- (9CI) (CA INDEX NAME)



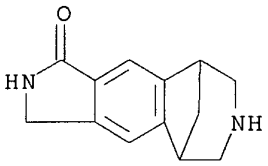
RN 287973-32-4 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepine-1,3(2H,5H)-dione, 5,6,7,8-tetrahydro- (9CI) (CA INDEX NAME)



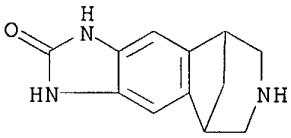
RN 328055-77-2 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



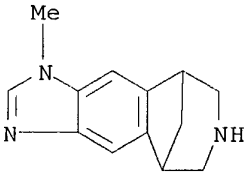
RN 328055-78-3 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



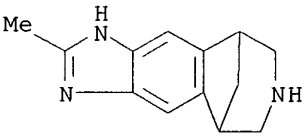
RN 328055-79-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



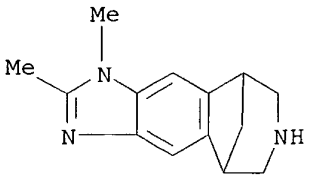
RN 328055-87-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl- (9CI) (CA INDEX NAME)



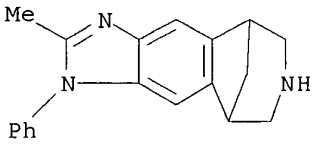
RN 328055-88-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



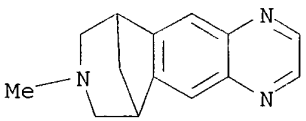
RN 328055-89-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl- (9CI) (CA INDEX NAME)



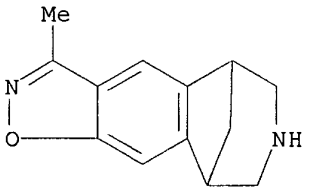
RN 328055-90-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl- (9CI) (CA INDEX NAME)



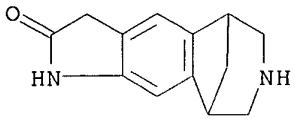
RN 328055-92-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl- (9CI) (CA INDEX NAME)



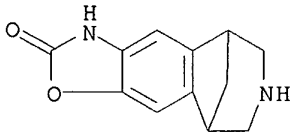
RN 328055-98-7 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl- (9CI) (CA INDEX NAME)



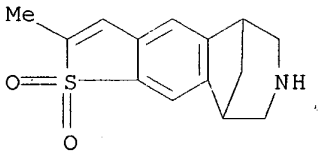
RN 357424-02-3 CAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



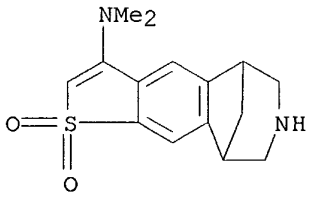
RN 357424-03-4 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



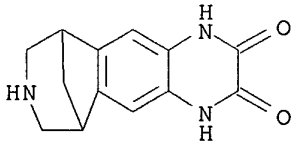
RN 357424-05-6 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, 1,1-dioxide (9CI) (CA INDEX NAME)



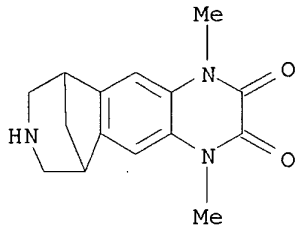
RN 357424-06-7 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepin-3-amine, 6,7,8,9-tetrahydro-N,N-dimethyl-, 1,1-dioxide (9CI) (CA INDEX NAME)



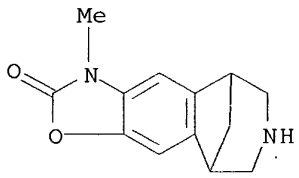
RN 357424-07-8 CAPLUS
CN 6,10-Methano-1H-pyrazino[2,3-h][3]benzazepine-2,3-dione, 4,6,7,8,9,10-hexahydro- (9CI) (CA INDEX NAME)



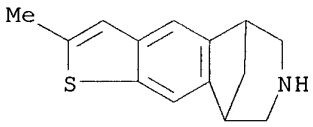
RN 357424-08-9 CAPLUS
CN 6,10-Methano-1H-pyrazino[2,3-h][3]benzazepine-2,3-dione, 4,6,7,8,9,10-hexahydro-1,4-dimethyl- (9CI) (CA INDEX NAME)



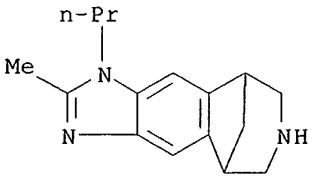
RN 357424-09-0 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-3-methyl- (9CI) (CA INDEX NAME)



RN 357424-10-3 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)

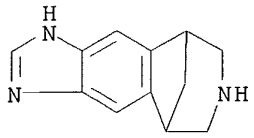


RN 357424-11-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-propyl- (9CI) (CA INDEX NAME)

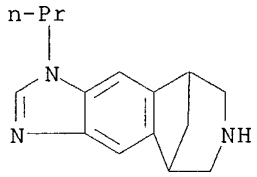


RN 357424-12-5 CAPLUS

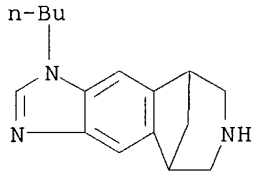
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



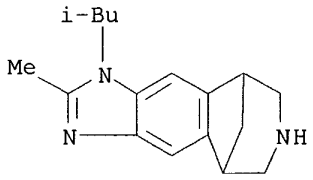
RN 357424-13-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-propyl- (9CI) (CA INDEX NAME)



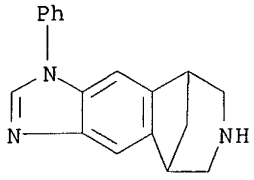
RN 357424-14-7 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-butyl-1,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



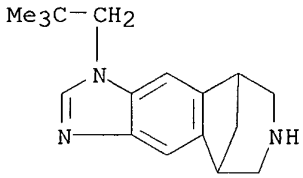
RN 357424-15-8 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-(2-methylpropyl)- (9CI) (CA INDEX NAME)



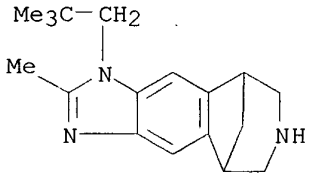
RN 357424-16-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-phenyl- (9CI) (CA INDEX NAME)



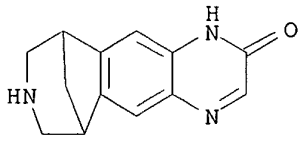
RN 357424-17-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



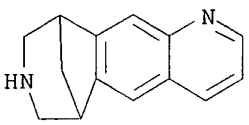
RN 357424-18-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



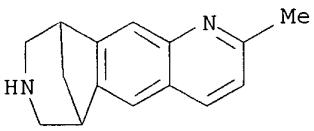
RN 357424-21-6 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro- (9CI) (CA INDEX NAME)



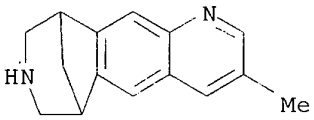
RN 357424-36-3 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



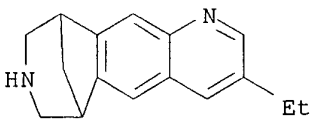
RN 357424-37-4 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



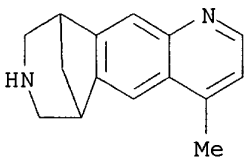
RN 357424-39-6 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-3-methyl- (9CI) (CA INDEX NAME)



RN 357424-41-0 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 3-ethyl-7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)

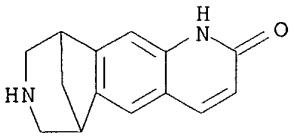


RN 357424-43-2 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-4-methyl- (9CI) (CA INDEX NAME)

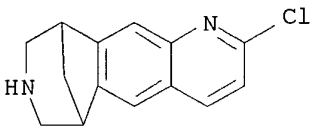


RN 357424-45-4 CAPLUS

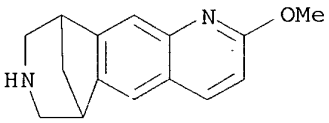
CN 6,10-Methano-2H-pyrido[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro- (9CI) (CA INDEX NAME)



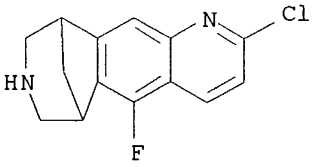
RN 357424-47-6 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



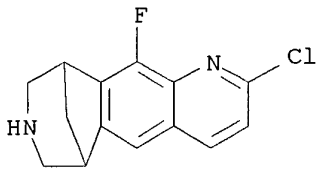
RN 357424-49-8 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methoxy- (9CI) (CA INDEX NAME)



RN 357424-51-2 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-5-fluoro-7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)

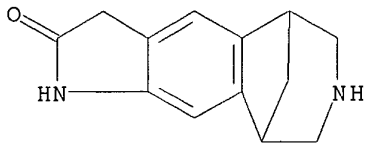


RN 357424-53-4 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-11-fluoro-7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



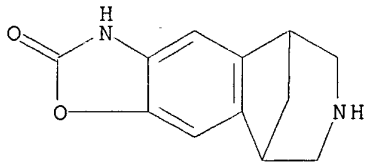
RN 357424-55-6 CAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



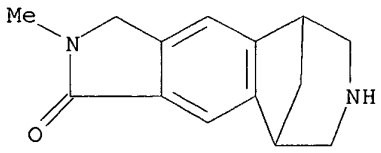
RN 357424-57-8 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



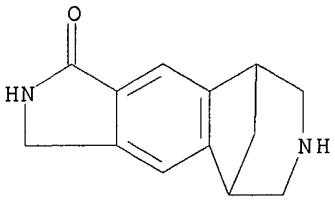
RN 357424-61-4 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-2-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



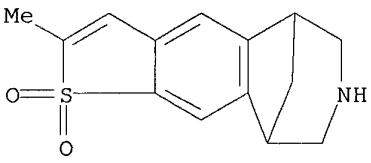
RN 357424-62-5 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



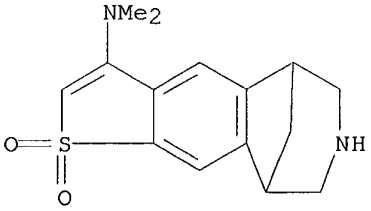
RN 357424-63-6 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, 1,1-dioxide, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



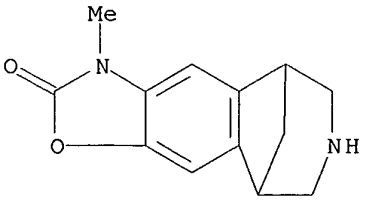
RN 357424-64-7 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepin-3-amine, 6,7,8,9-tetrahydro-N,N-dimethyl-, 1,1-dioxide, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



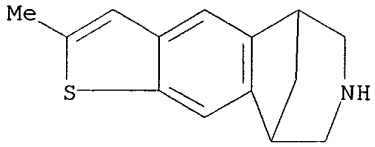
RN 357424-65-8 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-3-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



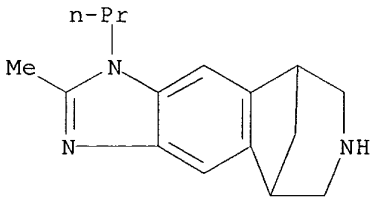
RN 357424-67-0 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



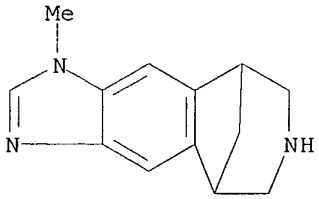
RN 357424-68-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-propyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



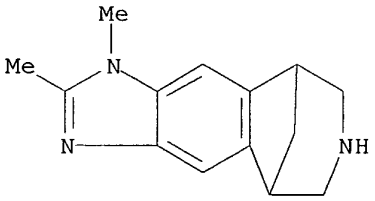
RN 357424-69-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



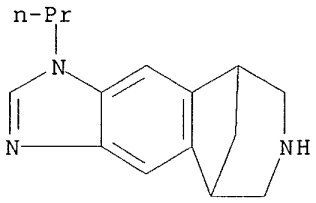
RN 357424-70-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



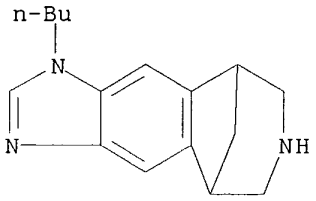
RN 357424-71-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-propyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



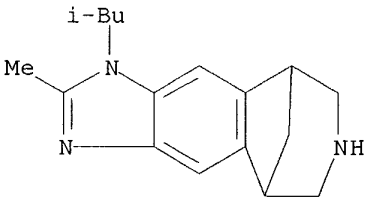
RN 357424-72-7 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-butyl-1,5,6,7,8,9-hexahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



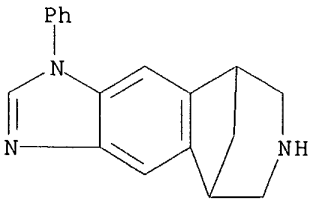
RN 357424-73-8 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-(2-methylpropyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



RN 357424-74-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-phenyl-, (+)- (9CI) (CA INDEX NAME)

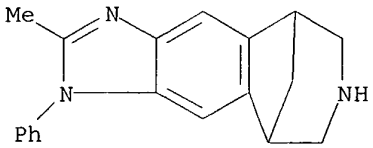
Rotation (+).



RN 357424-75-0 CAPLUS

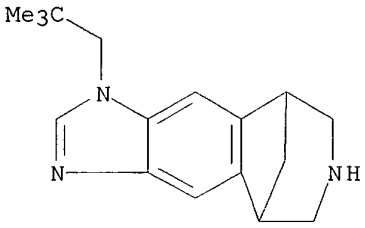
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



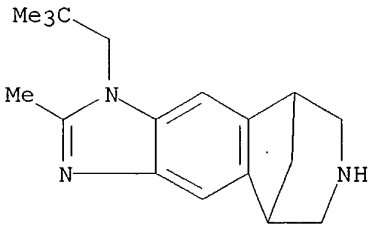
RN 357424-76-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



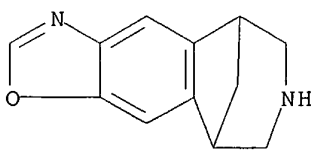
RN 357424-77-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-2-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



RN 357424-78-3 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-, (+)- (9CI) (CA INDEX NAME)

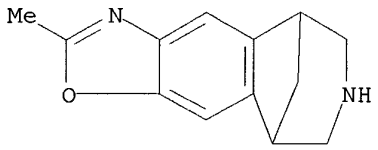
Rotation (+).



RN 357424-79-4 CAPLUS

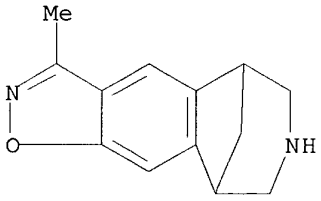
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



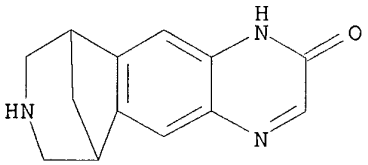
RN 357424-80-7 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



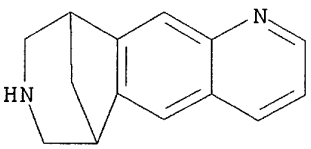
RN 357424-81-8 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



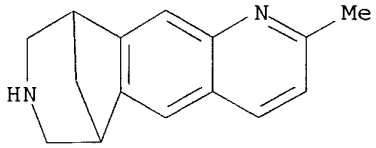
RN 357425-07-1 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



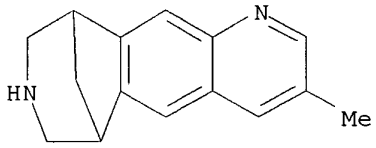
RN 357425-09-3 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



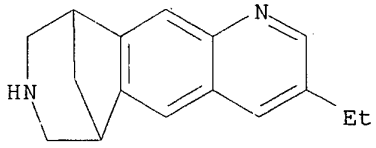
RN 357425-10-6 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-3-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



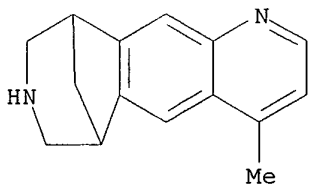
RN 357425-12-8 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 3-ethyl-7,8,9,10-tetrahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



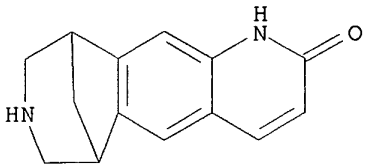
RN 357425-13-9 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-4-methyl-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



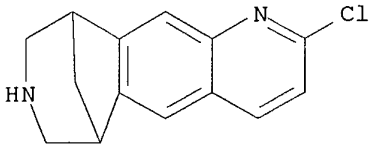
RN 357425-15-1 CAPLUS
CN 6,10-Methano-2H-pyrido[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



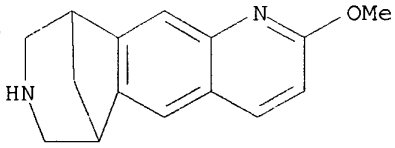
RN 357425-17-3 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-7,8,9,10-tetrahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



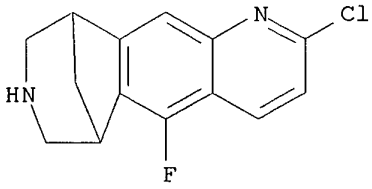
RN 357425-18-4 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methoxy-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



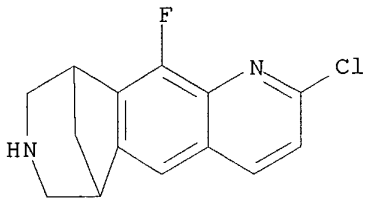
RN 357425-20-8 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-5-fluoro-7,8,9,10-tetrahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



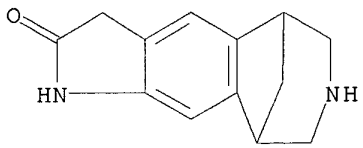
RN 357425-22-0 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-11-fluoro-7,8,9,10-tetrahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



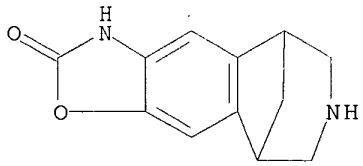
RN 357425-24-2 CAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



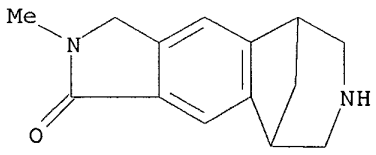
RN 357425-26-4 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



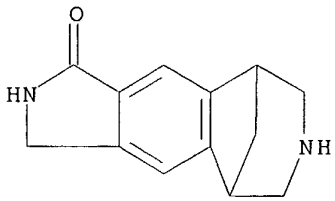
RN 357425-28-6 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-2-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



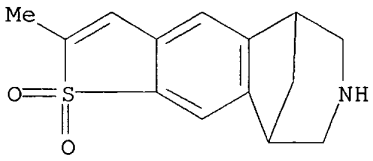
RN 357425-29-7 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



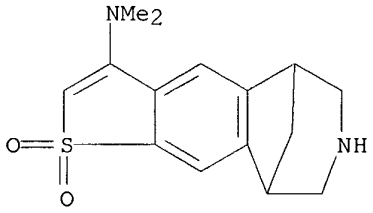
RN 357425-30-0 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, 1,1-dioxide, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



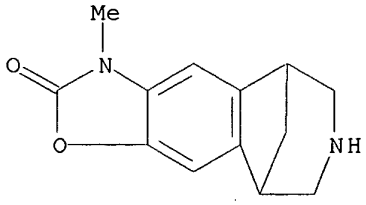
RN 357425-31-1 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepin-3-amine, 6,7,8,9-tetrahydro-N,N-dimethyl-, 1,1-dioxide, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



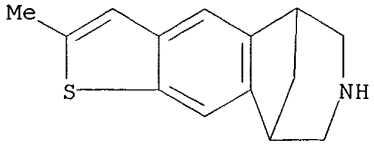
RN 357425-32-2 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-3-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



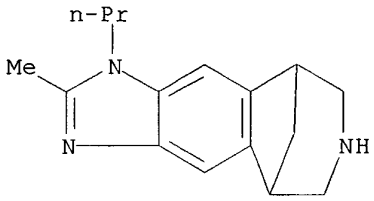
RN 357425-34-4 CAPLUS
CN 5,9-Methano-5H-thieno[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



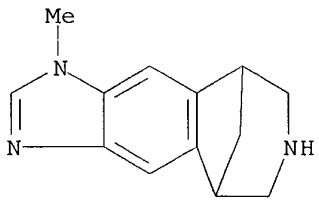
RN 357425-35-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-propyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



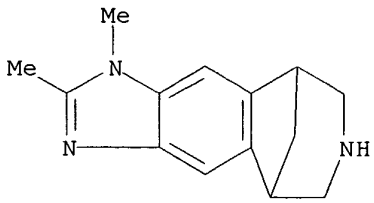
RN 357425-36-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



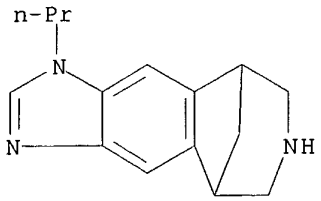
RN 357425-37-7 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



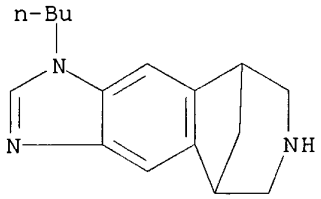
RN 357425-38-8 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-propyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



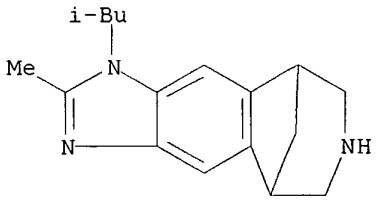
RN 357425-39-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-butyl-1,5,6,7,8,9-hexahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



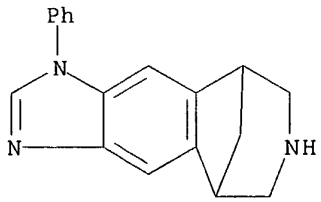
RN 357425-40-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-(2-methylpropyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



RN 357425-41-3 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-phenyl-, (-)- (9CI) (CA INDEX NAME)

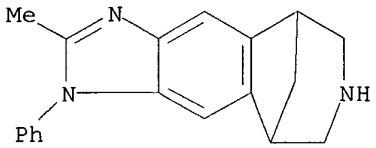
Rotation (-).



RN 357425-42-4 CAPLUS

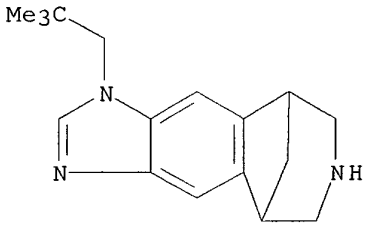
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



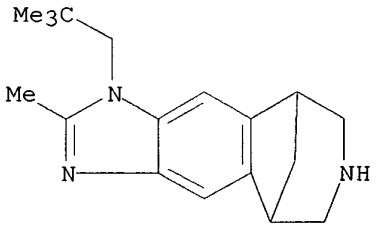
RN 357425-43-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



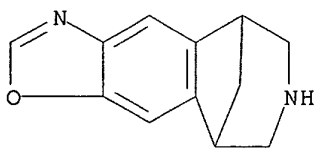
RN 357425-44-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-2-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



RN 357425-45-7 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-, (-)- (9CI) (CA INDEX NAME)

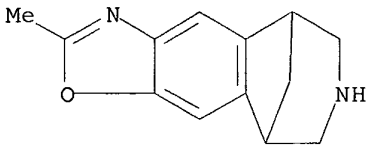
Rotation (-).



RN 357425-46-8 CAPLUS

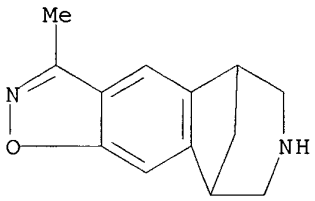
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



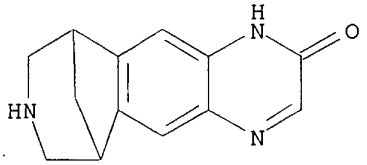
RN 357425-47-9 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



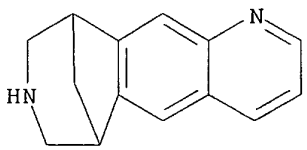
RN 357425-48-0 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



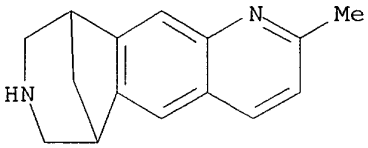
RN 357425-72-0 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



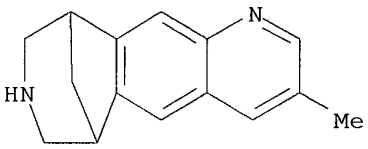
RN 357425-73-1 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



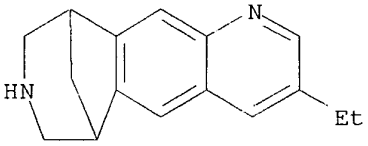
RN 357425-74-2 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-3-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



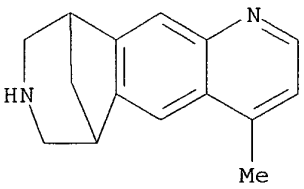
RN 357425-75-3 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 3-ethyl-7,8,9,10-tetrahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



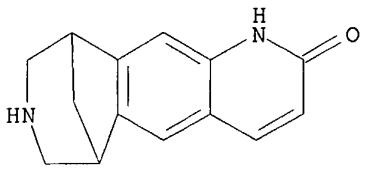
RN 357425-76-4 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-4-methyl-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



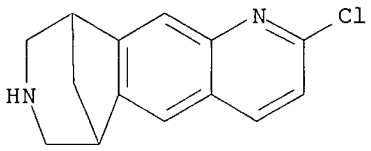
RN 357425-77-5 CAPLUS
CN 6,10-Methano-2H-pyrido[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



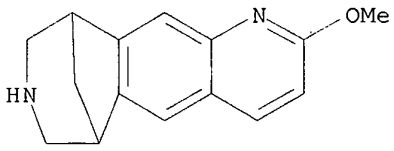
RN 357425-78-6 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-7,8,9,10-tetrahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



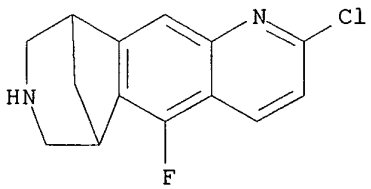
RN 357425-79-7 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methoxy-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



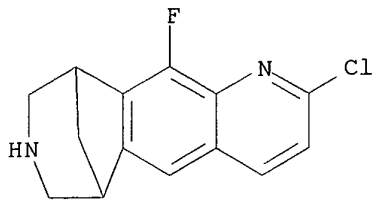
RN 357425-80-0 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-5-fluoro-7,8,9,10-tetrahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).

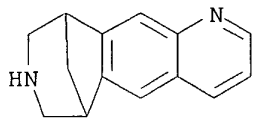


RN 357425-81-1 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-11-fluoro-7,8,9,10-tetrahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).

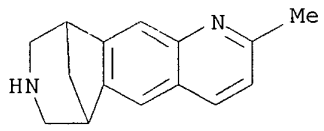


RN 357425-82-2 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, dihydrochloride (9CI) (CA INDEX NAME)



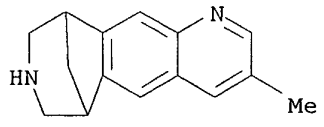
●2 HCl

RN 357425-83-3 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



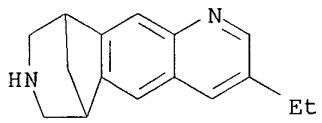
●2 HCl

RN 357425-84-4 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-3-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



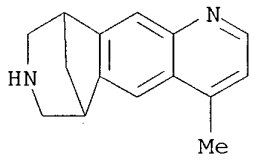
● HCl

RN 357425-86-6 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 3-ethyl-7,8,9,10-tetrahydro-, dihydrochloride (9CI) (CA INDEX NAME)



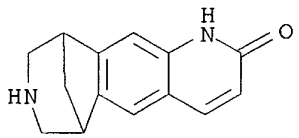
●2 HCl

RN 357425-87-7 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-4-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



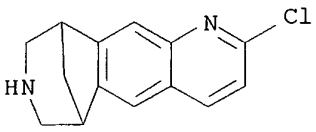
●2 HCl

RN 357425-88-8 CAPLUS
CN 6,10-Methano-2H-pyrido[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, dihydrochloride (9CI) (CA INDEX NAME)



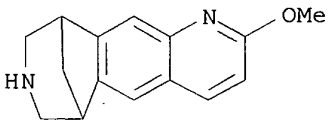
●2 HCl

RN 357425-89-9 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-7,8,9,10-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



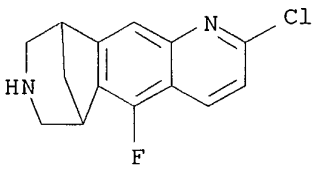
● HCl

RN 357425-90-2 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methoxy-, monohydrochloride (9CI) (CA INDEX NAME)



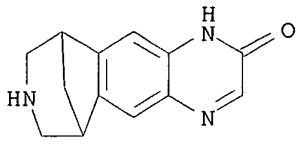
● HCl

RN 357425-91-3 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-5-fluoro-7,8,9,10-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



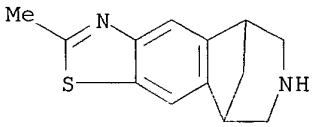
● HCl

RN 357425-92-4 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)

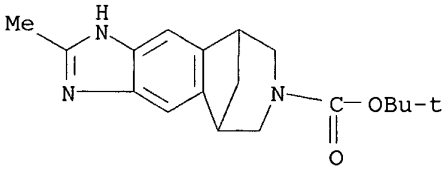


● HCl

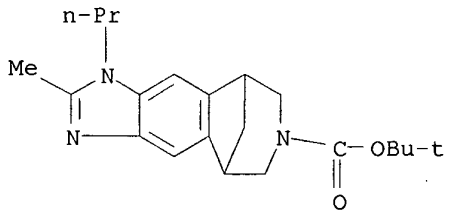
IT **357426-16-5**
RL: RCT (Reactant)
(prepn. of aryl-fused azapolycyclic compds. as nicotine binding inhibitors)
RN 357426-16-5 CAPLUS
CN 5,9-Methano-5H-thiazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



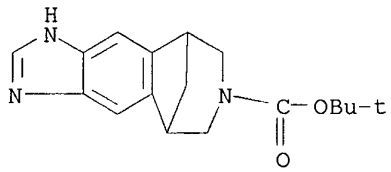
IT **230615-62-0P 230615-63-1P 230615-64-2P**
230615-67-5P 230615-68-6P 230615-70-0P
230615-73-3P 230615-74-4P 230615-86-8P
357425-95-7P 357425-98-0P 357425-99-1P
357426-00-7P 357426-01-8P 357426-02-9P
357426-05-2P 357426-06-3P 357426-07-4P
357426-08-5P 357426-09-6P 357426-10-9P
357426-17-6P 357426-18-7P 357426-19-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of aryl-fused azapolycyclic compds. as nicotine binding inhibitors)
RN 230615-62-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



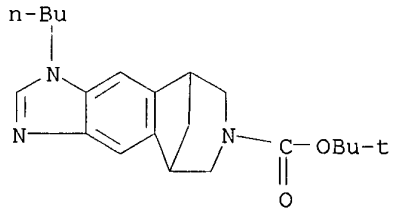
RN 230615-63-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-1-propyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



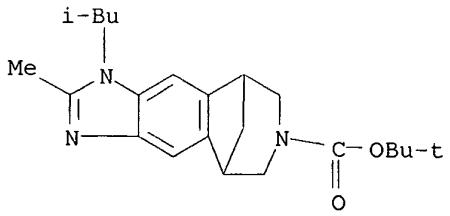
RN 230615-64-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-67-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 1-butyl-5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

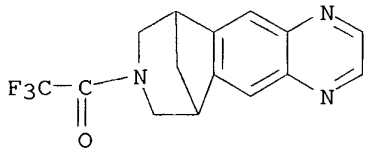


RN 230615-68-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-1-(2-methylpropyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

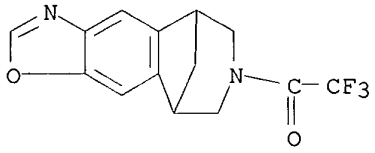


RN 230615-70-0 CAPLUS

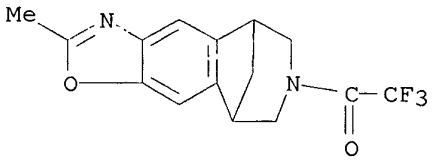
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



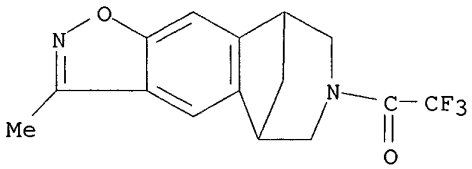
RN 230615-73-3 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



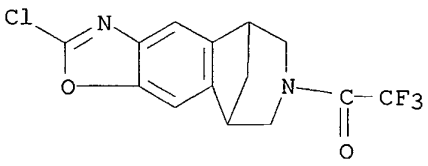
RN 230615-74-4 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



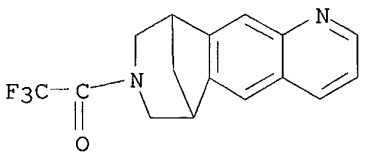
RN 230615-86-8 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



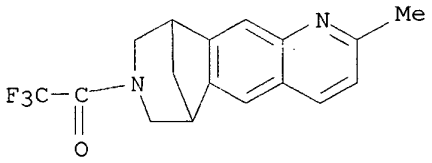
RN 357425-95-7 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 2-chloro-6,7,8,9-tetrahydro-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



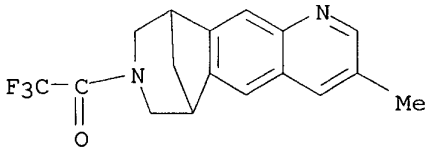
RN 357425-98-0 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



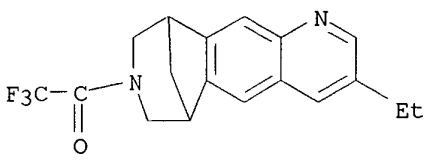
RN 357425-99-1 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2-methyl-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



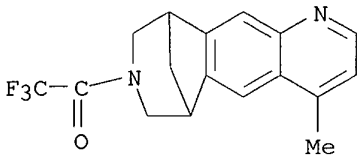
RN 357426-00-7 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-3-methyl-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



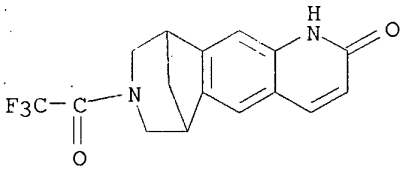
RN 357426-01-8 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 3-ethyl-7,8,9,10-tetrahydro-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



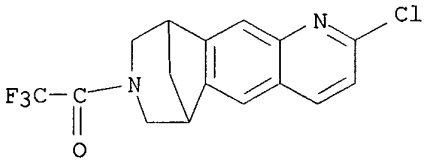
RN 357426-02-9 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-4-methyl-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



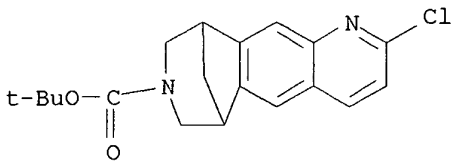
RN 357426-05-2 CAPLUS
CN 6,10-Methano-2H-pyrido[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



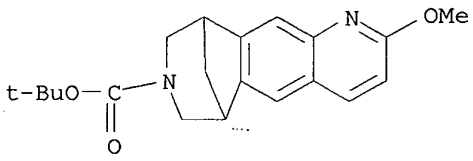
RN 357426-06-3 CAPLUS
CN 6,10-Methano-6H-pyrido[2,3-h][3]benzazepine, 2-chloro-7,8,9,10-tetrahydro-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



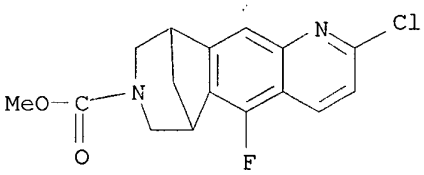
RN 357426-07-4 CAPLUS
CN 6,10-Methano-8H-pyrido[2,3-h][3]benzazepine-8-carboxylic acid, 2-chloro-6,7,9,10-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



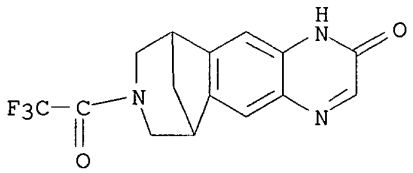
RN 357426-08-5 CAPLUS
CN 6,10-Methano-8H-pyrido[2,3-h][3]benzazepine-8-carboxylic acid, 6,7,9,10-tetrahydro-2-methoxy-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



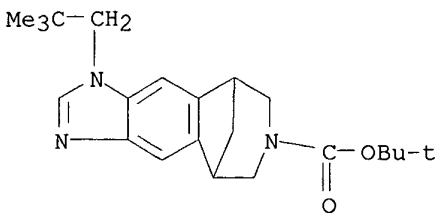
RN 357426-09-6 CAPLUS
CN 6,10-Methano-8H-pyrido[2,3-h][3]benzazepine-8-carboxylic acid, 2-chloro-5-fluoro-6,7,9,10-tetrahydro-, methyl ester (9CI) (CA INDEX NAME)



RN 357426-10-9 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

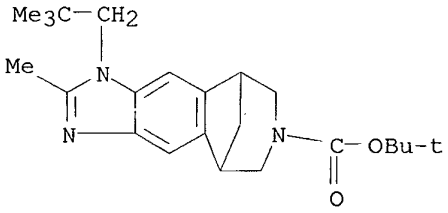


RN 357426-17-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 1-(2,2-dimethylpropyl)-5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester, monohydrochloride (9CI) (CA INDEX NAME)



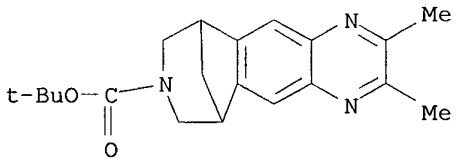
● HCl

RN 357426-18-7 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 1-(2,2-dimethylpropyl)-5,6,8,9-tetrahydro-2-methyl-, 1,1-dimethylethyl ester, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 357426-19-8 CAPLUS
CN 6,10-Methano-8H-pyrazino[2,3-h][3]benzazepine-8-carboxylic acid, 6,7,9,10-tetrahydro-2,3-dimethyl-, 1,1-dimethylethyl ester, monohydrochloride (9CI) (CA INDEX NAME)



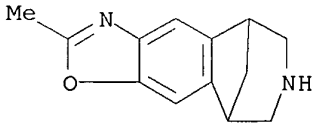
● HCl

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

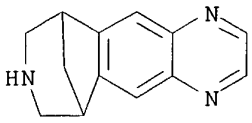
L23 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 2001:152263 CAPLUS
DN 134:198095
TI Composition for the treatment and prevention of nicotine addiction containing a nicotine receptor agonist and an anti-depressant or anti-anxiety drug
IN Coe, Jotham Wadsworth; Harrigan, Edmund Patrick; O'neill, Brian Thomas; Sands, Steven Bradley
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1078637	A2	20010228	EP 2000-307254	20000823
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001072604	A2	20010321	JP 2000-254041	20000824
PRAI US 1999-151089	P	19990827		

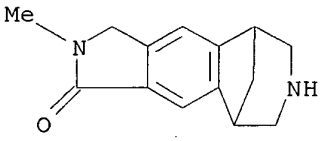
AB Pharmaceutical compns. are disclosed for the treatment of nicotine dependence or addiction, tobacco dependence or addiction, redn. of nicotine withdrawal symptoms or aiding in the cessation or lessening of tobacco use or substance abuse. The pharmaceutical compns. are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an anti-depressant or anxiolytic agent and a pharmaceutically acceptable carrier. The method of using these compds. is also disclosed.
IT **230615-75-5 249296-44-4 328055-77-2**
328055-78-3 328055-79-4 328055-83-0
328055-87-4 328055-88-5 328055-89-6
328055-90-9 328055-92-1 328055-93-2
328055-98-7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nicotine and other drug addiction treatment with compns. contg. nicotine receptor agonists and antidepressants or anxiolytic agents)
RN 230615-75-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



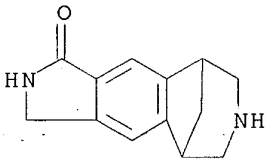
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



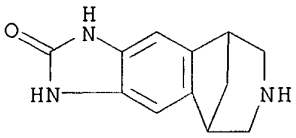
RN 328055-77-2 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



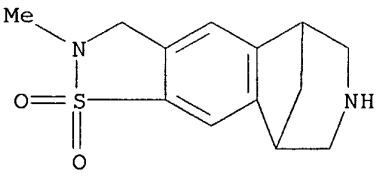
RN 328055-78-3 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepin-1(2H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



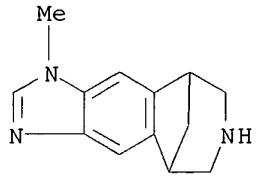
RN 328055-79-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



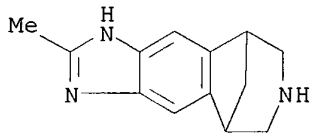
RN 328055-83-0 CAPLUS
CN 5,9-Methano-2H-isothiazolo[4,5-h][3]benzazepine, 3,5,6,7,8,9-hexahydro-2-methyl-, 1,1-dioxide (9CI) (CA INDEX NAME)



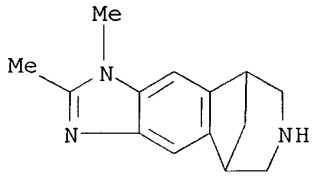
RN 328055-87-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl- (9CI) (CA INDEX NAME)



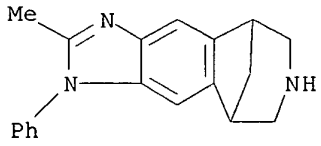
RN 328055-88-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



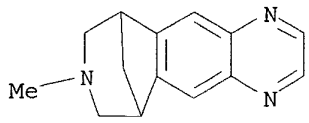
RN 328055-89-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl- (9CI) (CA INDEX NAME)



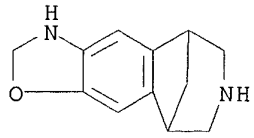
RN 328055-90-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl- (9CI) (CA INDEX NAME)



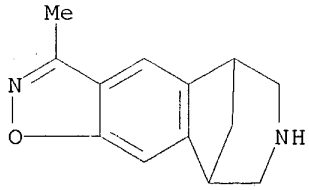
RN 328055-92-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl- (9CI) (CA INDEX NAME)



RN 328055-93-2 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepine, 3,5,6,7,8,9-hexahydro- (9CI) (CA INDEX NAME)



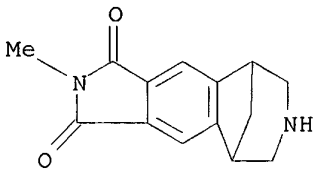
RN 328055-98-7 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl- (9CI) (CA INDEX NAME)



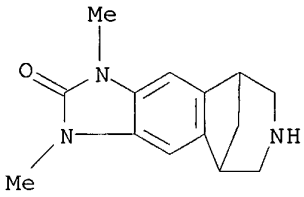
L23 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 2000:553442 CAPLUS
DN 133:168383
TI Pharmaceutical compositions containing nicotine or a ligand of nicotine receptors and a monamine oxidase inhibitor and their use for treating tobacco withdrawal symptoms
IN Caille, Dominique; George, Pascal; Jegham, Samir; Robineau, Pascale; Scatton, Bernard; Zivkovic, Branimir
PA Sanofi-Synthelabo, Fr.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT **Patent**
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000045846	A1	20000810	WO 2000-FR193	20000128
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2788982	A1	20000804	FR 1999-1144	19990202
EP 1150715	A1	20011107	EP 2000-901660	20000128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI FR 1999-1144	A	19990202		
WO 2000-FR193	W	20000128		

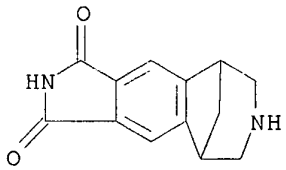
OS MARPAT 133:168383
AB The invention concerns novel pharmaceutical compns. contg. nicotine or a ligand of nicotine receptors and a monamine oxidase inhibitor designed for treating tobacco withdrawal symptoms. A bilayer tablet contained befloxatone 5, lactose 66, microcryst. cellulose 20, povidone 4, crospovidone 4, and magnesium stearate 1% in the first layer, and nicotine polacrylix 5, microcryst. cellulose 20 povidone 4, hydroxypropyl Me cellulose 25, magnesium stearate 1, and lactose q.s. 100% in the second layer.
IT **287973-24-4 287973-25-5 287973-32-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. nicotine or ligand of nicotine receptors and monamine oxidase inhibitor and their use for treating tobacco withdrawal symptoms)
RN 287973-24-4 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepine-1,3(2H,5H)-dione, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



RN 287973-25-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-1,3-dimethyl- (9CI) (CA INDEX NAME)



RN 287973-32-4 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepine-1,3(2H,5H)-dione, 5,6,7,8-tetrahydro- (9CI) (CA INDEX NAME)



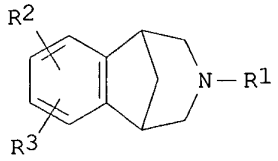
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

applicants

L23 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1999:451282 CAPLUS
DN 131:102204
TI Preparation of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands
IN Coe, Jotham Wadsworth; Brooks, Paige Roanne Palmer
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9935131	A1	19990715	WO 1998-IB1813	19981113
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9896416	A1	19990726	AU 1998-96416	19981113
	BR 9814592	A	20001017	BR 1998-14592	19981113
	EP 1044189	A1	20001018	EP 1998-950274	19981113
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
	JP 2002500218	T2	20020108	JP 2000-527532	19981113
	NO 2000003422	A	20000829	NO 2000-3422	20000630
PRAI	US 1997-70245	P	19971231		
	WO 1998-IB1813	W	19981113		

OS MARPAT 131:102204
GI



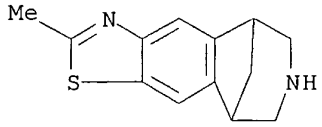
I

AB Title compds. [I; R1 = H, alk(en)yl, alkoxyethyl, oxoalkyl, etc.; R2,R3 = H, halo, (di)(alkyl)amino, alkyl, etc.; R2R3 = atoms to complete a ring] were prepd. Thus, 2-FC6H4Br was cyclocondensed with cyclopentadiene and the product osmylated to give 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol which was treated with NaIO4 and the product cyclocondensed with PhCH2NH2 to give, after deprotection, I (R1-R3 = H). Data for biol. activity of I were given.

IT **230615-07-3P 230615-09-5P 230615-10-8P**
230615-11-9P 230615-12-0P 230615-13-1P
230615-14-2P 230615-15-3P 230615-16-4P
230615-17-5P 230615-18-6P 230615-19-7P
230615-20-0P 230615-21-1P 230615-22-2P
230615-23-3P 230615-24-4P 230615-25-5P

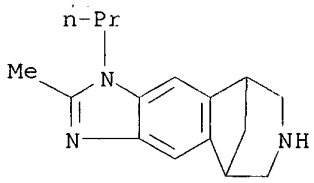
230615-26-6P 230615-33-5P 230615-39-1P
230615-40-4P 230615-44-8P 230615-45-9P
230615-46-0P 230615-75-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands)

RN 230615-07-3 CAPLUS
CN 5,9-Methano-5H-thiazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



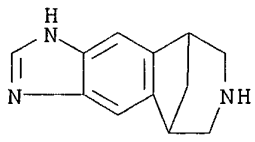
● HCl

RN 230615-09-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-propyl-, monohydrochloride (9CI) (CA INDEX NAME)



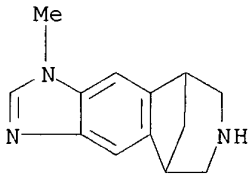
● HCl

RN 230615-10-8 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



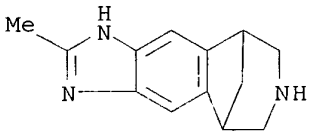
● HCl

RN 230615-11-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



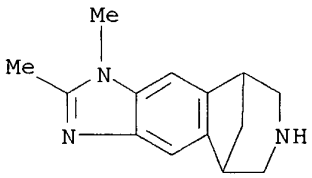
● HCl

RN 230615-12-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



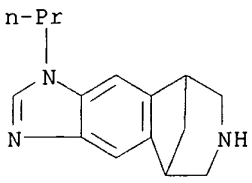
● HCl

RN 230615-13-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



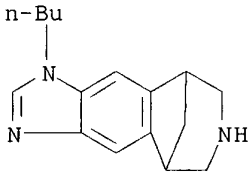
● HCl

RN 230615-14-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-propyl-, monohydrochloride (9CI) (CA INDEX NAME)



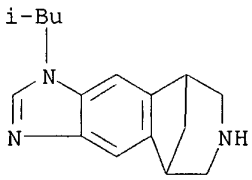
● HCl

RN 230615-15-3 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-butyl-1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



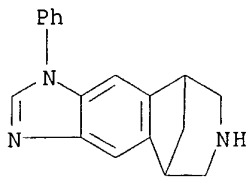
● HCl

RN 230615-16-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-(2-methylpropyl)-, monohydrochloride (9CI) (CA INDEX NAME)



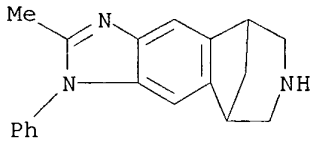
● HCl

RN 230615-17-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)



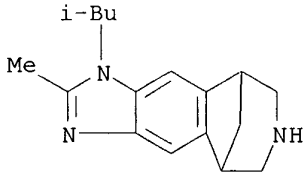
● HCl

RN 230615-18-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)



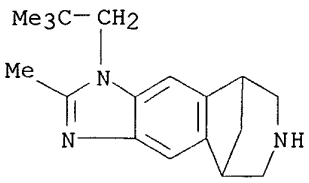
● HCl

RN 230615-19-7 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-(2-methylpropyl)-, monohydrochloride (9CI) (CA INDEX NAME)



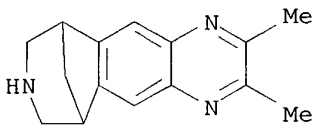
● HCl

RN 230615-20-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



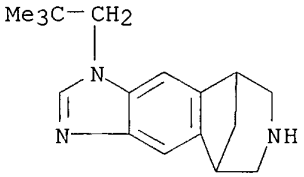
● HCl

RN 230615-21-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



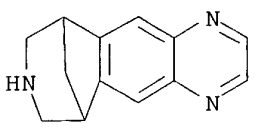
● HCl

RN 230615-22-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



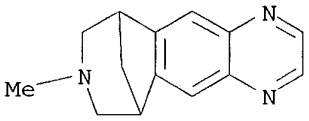
● HCl

RN 230615-23-3 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



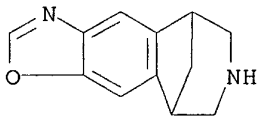
● HCl

RN 230615-24-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



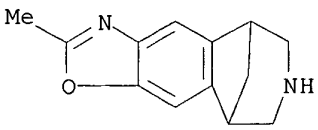
● HCl

RN 230615-25-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



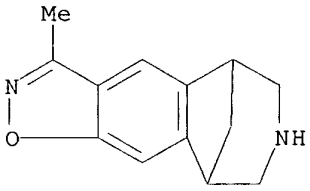
● HCl

RN 230615-26-6 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



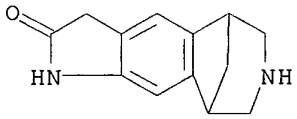
● HCl

RN 230615-33-5 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



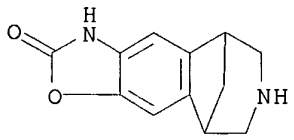
● HCl

RN 230615-39-1 CAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



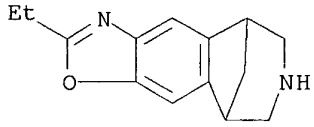
● HCl

RN 230615-40-4 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



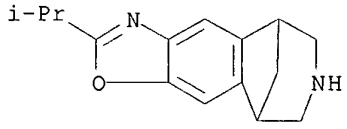
● HCl

RN 230615-44-8 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 2-ethyl-6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



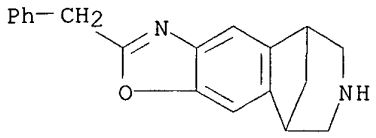
● HCl

RN 230615-45-9 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-(1-methylethyl)-, monohydrochloride (9CI) (CA INDEX NAME)



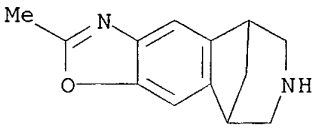
● HCl

RN 230615-46-0 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

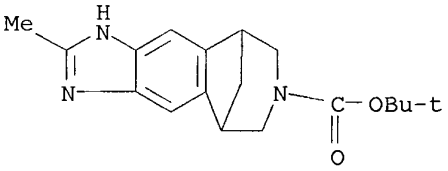


● HCl

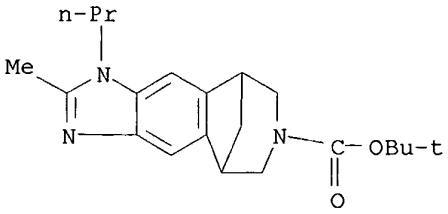
RN 230615-75-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



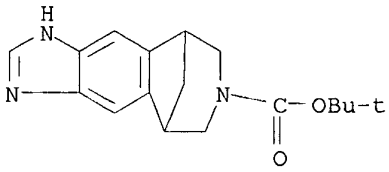
IT **230615-62-0P 230615-63-1P 230615-64-2P**
230615-67-5P 230615-68-6P 230615-70-0P
230615-73-3P 230615-74-4P 230615-86-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands)
RN 230615-62-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



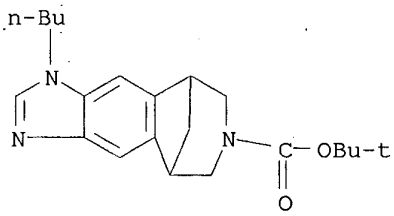
RN 230615-63-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-1-propyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



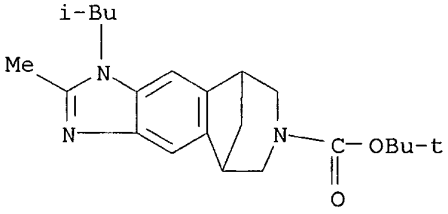
RN 230615-64-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-67-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 1-butyl-5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

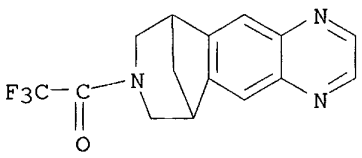


RN 230615-68-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-1-(2-methylpropyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

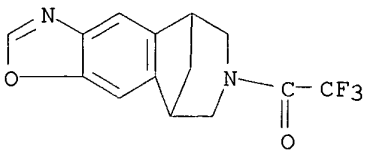


RN 230615-70-0 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-

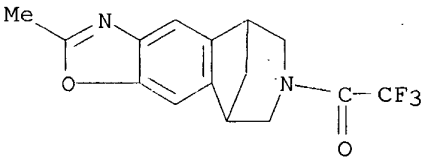
(trifluoroacetyl)- (9CI) (CA INDEX NAME)



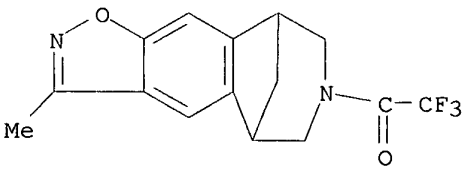
RN 230615-73-3 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-74-4 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-86-8 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Washington, D.C. 20231
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

7590 02/11/2002

PAUL H GINSBURG
PFIZER INC
235 EAST 42ND STREET
20TH FLOOR
NEW YORK, NY 100175755

EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	CLASS-SUBCLASS
1624	514-289000

DATE MAILED: 02/11/2002

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,010	09/28/1999	JOTHAM WADSWORTH COE	PC10030A	5433

TITLE OF INVENTION: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
15	nonprovisional	NO	$1280	$0	$1280	05/13/2002

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above. If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

B. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (REV. 07-01) Approved for use through 01/31/2004.

PART B - FEE(S) TRANSMITTAL

Complete and mail this form, together with applicable fee(s), to: **Box ISSUE FEE**
Assistant Commissioner for Patents
Washington, D.C. 20231

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

7590 02/11/2002

PAUL H GINSBURG
PFIZER INC
235 EAST 42ND STREET
20TH FLOOR
NEW YORK, NY 100175755

Note: The certificate of mailing below can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

Certificate of Mailing

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,010	09/28/1999	JOTHAM WADSWORTH COE	PC10030A	5433

TITLE OF INVENTION: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
15	nonprovisional	NO	$1280	$0	$1280	05/13/2002

EXAMINER	ART UNIT	CLASS-SUBCLASS
COLEMAN, BRENDA LIBBY	1624	514-289000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47) attached.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) ❑ individual ❑ corporation or other private group entity ❑ government

4a. The following fee(s) are enclosed:

❑ Issue Fee

❑ Publication Fee

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s):

❑ A check in the amount of the fee(s) is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Commissioner is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____(enclose an extra copy of this form).

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE; The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, United States Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington, D.C. 20231

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,010	09/28/1999	JOTHAM WADSWORTH COE	PC10030A	5433

7590 02/11/2002

PAUL H GINSBURG
PFIZER INC
235 EAST 42ND STREET
20TH FLOOR
NEW YORK, NY 100175755

EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/11/2002

Determination of Patent Term Extension under 35 U.S.C. 154 (b)

(application filed after June 7, 1995 but prior to May 29, 2000)

The patent term extension is 0 days. Any patent to issue from the above identified application will include an indication of the 0 day extension on the front page.

If a continued prosecution application (CPA) was filed in the above-identified application, the filing date that determines patent term extension is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system. (http://pair.uspto.gov)

PTOL-85 (REV. 07-01) Approved for use through 01/31/2004.

Notice of Allowability

Application No.	Applicant(s)
09/402,010	COE et al.
Examiner	**Art Unit**
Brenda Coleman	1624

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *December 3, 2001*.

2. ☒ The allowed claim(s) is/are *1, 2, 8-10, 14, 15, and 17-24*.

3. ☐ The drawings filed on _____ are acceptable as formal drawings.

4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____.
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   *Certified copies not received: _____.

5. ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS

   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No. _____.

   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.

   (c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

1 ☒ Notice of References Cited (PTO-892)
2 ☐ Notice of Informal Patent Application (PTO-152)
3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4 ☐ Interview Summary (PTO-413), Paper No. _____.
5 ☐ Information Disclosure Statement(s) (PTO-1449), Paper No(s). _____
6 ☐ Examiner's Amendment/Comment
7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8 ☐ Examiner's Statement of Reasons for Allowance
9 ☐ Other

Brenda Coleman

BRENDA COLEMAN
PRIMARY EXAMINER
ART UNIT 1624

Notice of References Cited	Applicant/Patent: COE et al.	Application/Control No.: 09/402,010	
	Examiner: Brenda Coleman	Art Unit: 1624	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY[1]	Name	Classification[2]	
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY[1]	Country	Name	Classification[2]	
x	N	EP 1 078 637	2/2001	EPO	COE et al.	----	----
x	O	EP 0 955 301	11/1999	EPO	YOHANNES et al.	----	----
x	P	WO 00/45846	8/2000	WIPO	CAILLE et al.	----	----
x	Q	WO 00/44755	8/2000	WIPO	BUNNELLE et al.	----	----
x	R	WO 99/55680	11/1999	WIPO	COE	----	----
	S						
	T						

NON-PATENT DOCUMENTS

*		Include, as applicable: Author, Title, Date, Publisher, Edition or Volume, Pertinent Pages
	U	
	V	
	W	
	X	

* A copy of this reference is not being furnished with this Office action. See MPEP § 707.05(a). [1] Dates in MM-YYYY format are publication dates. [2] Classifications may be U.S. or foreign.

Brenda Coleman

B/FF

PART B - FEE(S) TRANSMITTAL

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Washington, D.C. 20231

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CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

7590 02/11/2002

PAUL H GINSBURG
PFIZER INC
235 EAST 42ND STREET
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Roy F. Waldron (Depositor's name)
(Signature)
May 8, 2002 (Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,010	09/28/1999	JOTHAM WADSWORTH COE	PC10030A	5433

TITLE OF INVENTION: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
15	nonprovisional	NO	$1280	$0	$1280	05/13/2002

EXAMINER	ART UNIT	CLASS-SUBCLASS
COLEMAN, BRENDA LIBBY	1624	514-289000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

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2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Peter C. Richardson
2 Paul H. Ginsburg
3 Roy F. Waldron

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: PFIZER INC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): NEW YORK, N.Y.

Please check the appropriate assignee category or categories (will not be printed on the patent) ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

☒ Issue Fee
☒ Publication Fee
☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.
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☒ The Commissioner is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 16-1445 (enclose an extra copy of this form).

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date) May 3, 2002

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, United States Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington, D.C. 20231

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01 FC:195 300.00 CH

TRANSMIT THIS FORM WITH FEE(S)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	**U.S. PATENT NO. 6,410,550**
ISSUED:	**JUNE 25, 2002**
TO:	**JOTHAM W. COE AND PAIGE R.P. BROOKS**
FOR:	**ARYL FUSED AZAPOLYCYCLIC COMPOUNDS**
FROM:	**SERIAL NO. 09/402,010**
OF:	**Nov. 13, 1998**

Via Federal Express
Madison West Bldg.
600 Dulaney St. 7D-55
Alexandria, VA 22314

Attention: Mary Till

Madam:

TRANSMITTAL OF REPLACEMENT COPIES OF REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Enclosed are replacement copies of the application papers of PFIZER INC., dated June 28, 2006, for extension of the term of U.S. Patent No. 6,410,550 under 35 U.S.C. §156, based on the regulatory review period for CHANTIX™ (varenicline) Tablets, together with two duplicate copies as required under 37 C.F.R. §1.740(b) and two additional duplicate copies of the application pursuant to M.P.E.P. §2753, for a total of five copies which were originally submitted June 28, 2006. A copy of the Postcard receipt stamped by USPTO Mail Room is also enclosed indicating receipt of the original papers by the USPTO on June 28, 2006.

Respectfully submitted,
PFIZER INC.

Date: October 24, 2006

A. David Joran
Attorney for Applicant
Reg. No. 37,858

PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755
Tel.: (212) 733-3381
Fax: (212) 573-1939

Legal Division
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

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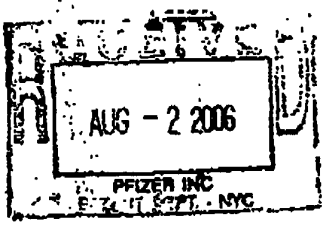
Note: Enclosed is the Postcard of PC10030A.



Date: June 28, 2006 Express Mail No. BY HAND

US Patent No. 6,410,550 Docket No. PC10030A By ADJ

Application of Jotham W. Coe et al Filing Date Nov. 13, 1998

Entitled Aryl Fused Azapolycyclic Compounds

The following, has been received by the United States Patent and Trademark Office on the date stamped hereon:

- ☐ Application Transmittal *Type:*
- ☐ Specification *pages*
- ☐ Claims *pages*
- ☐ Abstract *pages*
- ☐ Drawing(s) *sheets*
- ☒ Power of Attorney and Correspondence Address Form
- ☒ Statement Under 37CFR 3.73 (b)
- ☒ Application for Extension of the Term of United States Patent No. 6,410,550 Under 35 U.S.C. §156
- ☒ Transmittal of Request for Extension of Patent Term Under 35 U.S.C. §156
- ☐ Notice of Appeal
- ☐ Brief (3 copies)
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Certificate of Correction
- ☐ Petition for Extension of Time
- ☐ Fee Transmittal (2 copies)
- ☐ Associate Power of Attorney
- ☐ Petition for Expedited Issuance for Foreign Filing License
- ☒ EXHIBITS A through D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	U.S. PATENT NO. 6,410,550
ISSUED:	JUNE 25, 2002
TO:	JOTHAM W. COE AND PAIGE R.P. BROOKS
FOR:	ARYL FUSED AZAPOLYCYCLIC COMPOUNDS
FROM:	SERIAL NO. 09/402,010
OF:	Nov. 13, 1998

Commissioner for Patents
Mail Stop Patent Ext.
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

TRANSMITTAL OF REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Transmitted herewith are the application papers of PFIZER INC., dated June 28, 2006, for extension of the term of U.S. Patent No. 6,410,550 under 35 U.S.C. §156, based on the regulatory review period for CHANTIX™ (varenicline) Tablets, together with two duplicate copies as required under 37 C.F.R. §1.740(b) and two additional duplicate copies of the application pursuant to M.P.E.P. §2753, for a total of four copies and one original.

As set forth under 37 C.F.R. §1.20(j), please charge the sum of $1,120.00 to Deposit Account No. 16-1445 for the filing of this application for extension of patent term. Also, please charge any underpayment, or any additional fees that may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,
PFIZER INC.

Date: June 28, 2006

A. David Joran
Attorney for Applicant
Reg. No. 37,858

PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755
Tel.: (212) 733-3381
Fax: (212) 573-1939

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	U.S. PATENT NO. 6,410,550
ISSUED:	JUNE 25, 2002
TO:	JOTHAM W. COE AND PAIGE R.P. BROOKS
FOR:	ARYL FUSED AZAPOLYCYCLIC COMPOUNDS
FROM:	SERIAL NO. 09/402,010
OF:	Nov. 13, 1998

Commissioner for Patents
Mail Stop Patent Ext.
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

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Transmitted herewith are the application papers of PFIZER INC., dated June 28, 2006, for extension of the term of U.S. Patent No. 6,410,550 under 35 U.S.C. §156, based on the regulatory review period for CHANTIX™ (varenicline) Tablets, together with two duplicate copies as required under 37 C.F.R. §1.740(b) and two additional duplicate copies of the application pursuant to M.P.E.P. §2753, for a total of four copies and one original.

As set forth under 37 C.F.R. §1.20(j), please charge the sum of $1,120.00 to Deposit Account No. 16-1445 for the filing of this application for extension of patent term. Also, please charge any underpayment, or any additional fees that may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,
PFIZER INC.

Date: June 28, 2006

A. David Joran
Attorney for Applicant
Reg. No. 37,858

PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755
Tel.: (212) 733-3381
Fax: (212) 573-1939

PTO/SB/96 (12-05)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Pfizer Inc.

Application No./Patent No./Control No.: 09/402,010 Filed/Issue Date: September 28, 1999

Entitled: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Pfizer Inc (Name of Assignee), a Corporation (Type of Assignee: corporation, partnership, university, government agency, etc.)

states that it is:

1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest
(The extent (by percentage) of its ownership interest is _____%)

in the patent application/patent identified above by virtue of either:

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 012920, Frame 0128, or a true copy of the original assignment is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
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3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
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☐ Additional documents in the chain of title are listed on a supplemental sheet.

As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	Date
Grover F. Fuller Jr., Reg. No. 31,760	(212)-573-1390
Printed or Typed Name	Telephone Number
Senior Corporate Counsel of Pfizer Inc	
Title	

PTO/SB/81 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	09/402,010
Filing Date	September 28, 1999
First Named Inventor	Jotham Wadsworth Coe
Title	ARYL FUSED AZAPOLYCYCLIC COMPOUNI
Art Unit	
Examiner Name	
Attorney Docket Number	

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☑ Practitioners associated with the Customer Number: 23913

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

☑ The address associated with the above-mentioned Customer Number:

OR

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☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

☑ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature		Date	
Name	Grover F. Fuller Jr., Reg. No. 31,760	Telephone	212-573-1390
Title and Company	Senior Corporate Counsel of Pfizer Inc		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	U.S. PATENT NO. 6,410,550
ISSUED:	JUNE 25, 2002
TO:	JOTHAM W. COE AND PAIGE R.P. BROOKS
FOR:	ARYL FUSED AZAPOLYCYCLIC COMPOUNDS
FROM:	SERIAL NO. 09/402,010
OF:	Nov. 13, 1998

Commissioner for Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

APPLICATION FOR EXTENSION OF THE TERM OF UNITED STATES PATENT NO. 6,410,550 UNDER 35 U.S.C. §156 FOR CHANTIX™ (VARENICLINE) TABLETS

Your applicant, PFIZER INC., a corporation organized and existing under the laws of the State of Delaware, and having a place of business at 235 East 42nd Street, New York, NY 10017, United States of America, represents that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 6,410,550 granted to JOTHAM W. COE and PAIGE R.P. BROOKS on the 25th day of June, 2002, for ARYL FUSED AZAPOLYCYCLIC COMPOUNDS, by virtue of assignments, recorded in the United States Patent and Trademark Office (hereinafter referred to as "the Patent Office") on the 20th day of May, 2002 at Reel 012920, Frame 0128. A copy of the Notice of Recordation is enclosed as Exhibit A.

Pursuant to the provisions of 37 C.F.R. §1.730, your applicant hereby applies for an extension of the term of Patent No. 6,410,550 under 35 U.S.C. §156 of 545 days, based on the materials set forth herein and in the accompanying papers.

In the materials which follow herein, numbered paragraphs (1) through (15) correspond to paragraphs (1) through (15) of 37 C.F.R. §1.740(a).

(1) The approved product is the active ingredient, including any salt of the active ingredient, in CHANTIX™, *i.e.,* varenicline, varenicline tartrate, and any other pharmaceutically acceptable salt of varenicline, which is the generic name of the chemical compound. CHANTIX™ tablets consist of varenicline as the varenicline tartrate salt and pharmaceutically-acceptable carriers. Varenicline and varenicline tartrate are further identified as follows:

Varenicline:

Chemical Name

7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine

Alternate Chemical Name

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene

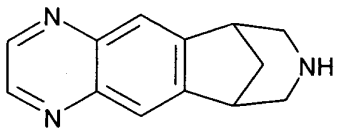
Molecular Formula

$C_{13}H_{13}N_3$

Molecular Weight

211.27

Chemical Formula



Varenicline tartrate:

Chemical Name

7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1)

Alternate Chemical Name

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene tartrate

Molecular Formula

$C_{13}H_{13}N_3 \bullet C_4H_6O_6$

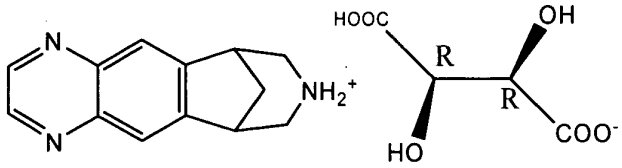
Molecular Weight

361.35

Physical Description

CHANTIX™ tablets are supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablets debossed with *"Pfizer"* on one side and "CHX 1.0" on the other side. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1mg CHANTIX™ tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

Chemical Formula



(2) CHANTIX™ (varenicline) tablets was subject to regulatory review under section 505(b) of the Federal Food, Drug and Cosmetic Act, which is codified at 21 U.S.C. §355(b).

(3) CHANTIX™ (varenicline) tablets received permission for commercial marketing or use under section 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(b), on May 10, 2006. It was approved as an aid to smoking cessation treatment.

(4) The active ingredient in CHANTIX™ tablets is varenicline, as its salt varenicline tartrate (5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene tartrate). Neither varenicline nor any salt thereof has been previously approved for

commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application could be submitted is July 10, 2006.

(6) The patent for which an extension is being sought is identified as follows:

Inventors:	JOTHAM W. COE AND PAIGE R.P. BROOKS
Patent No.:	6,410,550
For:	ARYL FUSED AZAPOLYCYCLIC COMPOUNDS
Issued:	JUNE 25, 2002
Expires:	NOVEMBER 13, 2018

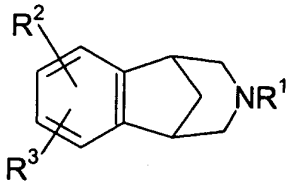
(7) A copy of Patent No. 6,410,550, the patent for which an extension is being sought, is attached hereto as EXHIBIT B.

(8) A maintenance fee payment for Patent No. 6,410,550 has been made to keep the patent in force beyond four years from its issue date. A copy of the official receipt for such payment is attached hereto as EXHIBIT C. Patent No. 6,410,550 has no disclaimers or re-examination certificates.

(9) Patent No. 6,410,550 claims the approved product, pharmaceutical compositions including the approved product, and a method of using the approved product. Claims 1 and 8 claim the approved product *per se*; claim 12 claims a pharmaceutical composition which contains the approved product and is useful for the approved use; and, claims 13 and 14 claim the approved use of the approved product. A showing that lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product, a pharmaceutical composition containing the approved product, or a method of using the approved product is as follows:

Claim 1 of Patent No. 6,410,550 reads as follows:

" A compound of the formula



(I)

R^1 is hydrogen, $(C_1\text{-}C_6)$alkyl, unconjugated $(C_3\text{-}C_6)$alkenyl, $XC(=O)R^{13}$, benzyl or $\text{-}CH_2CH_2\text{-}O\text{-}(C_1\text{-}C_4)$alkyl;

R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents that are selected, independently, from $(C_1\text{-}C_6)$ alkyl optionally substituted with from one to seven fluorine atoms; $(C_1\text{-}C_6)$alkoxy optionally substituted with from one to seven fluorine atoms; nitro, cyano, halo, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, amino, $(C_1\text{-}C_6)$alkylamino and $((C_1\text{-}C_6)\text{alkyl})_2$amino, $\text{-}CO_2R^4$, $\text{-}CONR^5R^6$, $\text{-}SO_2NR^7R^8$, $\text{-}C(=O)R^{13}$ and $\text{-}XC(=O)R^{13}$;

wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and $(C_1\text{-}C_6)$ alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-$(C_1\text{-}C_6)$alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, $(C_1\text{-}C_6)$alkylene;

or a pharmaceutically acceptable salt thereof."

When R_1 is hydrogen; and, R^2 and R^3, together with the carbons to which they are attached, form a six-membered monocyclic carbocyclic ring that is unsaturated, wherein two of the nonfused carbon atoms of said monocyclic ring are replaced by a nitrogen, and wherein the monocyclic ring is not substituted, the compound claimed is varenicline. Therefore, claim 1 reads on the approved product.

Claim 8 of Patent No. 6,410,550 claims the compound according to claim 1 which is 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene, which is varenicline. Claim 8 also claims a pharmaceutically acceptable salt 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene, which encompasses varenicline tartrate. Therefore, claim 8 reads on the approved product.

Claim 12 of Patent No. 6,410,550 claims a pharmaceutical composition comprising an amount of a compound according to claim 1 and a pharmaceutically acceptable carrier. Since claim 1 claims a compound which encompasses varenicline, claim 12 reads on a pharmaceutical composition comprising the approved product.

Claim 13 of Patent No. 6,410,550 claims a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use. Since claim 1 claims a compound which encompasses varenicline, claim 8 reads on a method of using the approved product for the approved use.

Claim 14 of Patent No. 6,410,550 claims a method for treating a disorder or condition selected from a grouping of indications which recites dependencies on, or addictions to, nicotine and tobacco products, comprising administering to a mammal in need of such treatment an amount of a compound according to claim 1 that is effective in treating such disorder or condition. Since claim 1 claims a compound, which encompasses varenicline, claim 14 reads on a method of using the approved product for the approved use.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

- An exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act became effective for varenicline tartrate October 14, 1999, following receipt by the Food and Drug Administration of Investigational New Drug ("IND") Application No. 58,994 on September 15, 1999.
- A New Drug Application ("NDA") under section 505(b) of the Federal Food, Drug and Cosmetic Act for CHANTIX™ was initially submitted on November 10, 2005, as NDA No. 21-928.
- NDA No. 21-928 was approved on May 10, 2006.

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as EXHIBIT D.

(12) Applicant is of the opinion that Patent No. 6,410,550 is eligible for an extension under 35 U.S.C. §156. The length of extension claimed is 545 days.

The eligibility requirements of 35 U.S.C. §§156(a) and 156(c)(4) have been satisfied as follows:

- Patent No. 6,410,550 claims a product (the active ingredient, including any salt of the active ingredient) in CHANTIX™, *i.e.,* varenicline, varenicline tartrate and any other pharmaceutically acceptable salt. Patent No. 6,410,550 also claims pharmaceutical compositions including the product CHANTIX™ and a method of using the product CHANTIX™.
- Patent No. 6,410,550 is currently set to expire on November 13, 2018 (*i.e.,* the term of the patent has not yet expired).
- The term of Patent No. 6,410,550 has never been extended under subsection (e)(1) of 35 U.S.C. §156.
- This application for extension is being submitted by PFIZER INC, the owner of record of Patent No. 6,410,550, in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. §156(d).
- The product (the active ingredient, including any salt of the active ingredient) in CHANTIX™, *i.e.,* varenicline, varenicline tartrate and any other pharmaceutically acceptable salt, has been subject to a regulatory review period under section 505(b) of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use, and the permission for said commercial marketing or use is the first permitted commercial marketing or use of the product under section 505(b) of the Federal Food, Drug and Cosmetic Act.
- No patent has to this date been extended, nor has any other extension been applied for, under subsection (e)(1) of 35 U.S.C. §156, for the regulatory review period which forms the basis for this application for extension of the term of Patent No. 6,410,550.

The length of extension of the term of Patent No. 6,410,550 of 545 days claimed by applicant was determined according to the provisions of 37 C.F.R. §1.775 as follows:

- According to 37 C.F.R. §1.775(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of 37 C.F.R. §1.775.
- According to 37 C.F.R. §1.775(c), the regulatory review period is the sum of: (A) the number of days in the period beginning on the date the exemption under subsection 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act; and (B) the number of days in the period beginning on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act and ending on the date the NDA was approved. The exemption under subsection 505(i) of the Federal Food, Drug and Cosmetic Act became effective on October 14, 1999; the NDA was initially submitted on November 10, 2005; and the NDA was approved on May 10, 2006. Hence, the regulatory review period under 37 C.F.R. §1.775(c) is the sum of the period from October 14, 1999 to November 10, 2005 and from November 10, 2005 to May 10, 2006. This is the sum of 2,219 days and 180 days, which is 2,399 days.
- According to 37 C.F.R. §1.775(d)(1)(i), the number of days in the regulatory review period which were on and before the date on which the patent issued must be subtracted. Patent No. 6,410,550 issued on June 25, 2002. Subtraction of the period on and before June 25, 2002 leaves a reduced regulatory review period from June 26, 2002 to November 10, 2005 and from November 10, 2005 to May 10, 2006. This is the sum of 1,234 days and 180 days, which is 1,414 days.
- 37 C.F.R. §1.775(d)(1)(ii) does not apply.
- According to 37 C.F.R. §1.775(d)(1)(iii), the regulatory review period must then be reduced by one-half of the days remaining in the period defined in 37 C.F.R. §1.775(c)(1). This is one-half of 1,234 days, which is 617 days. After subtraction, this now leaves a reduced regulatory review period of 617 days plus 180 days, which is 797 days.

- According to 37 C.F.R. §1.775(d)(2), the reduced regulatory review period of 797 days must be added to the expiration date of Patent No. 6,410,550 (*i.e.,* November 13, 2018). This gives a date of July 22, 2020. According to 37 C.F.R. §1.775(d)(3), 14 years must be added to the date of approval of the approved product. This gives a date of May 10, 2020. According to 37 C.F.R. §1.775(d)(4), the earlier of these dates must be selected. The earlier of these dates is May 10, 2020 (*i.e.,* 545 days beyond the expiration date of the 6,410,550 patent).
- The provisions of 37 C.F.R. §1.775(d)(5) apply to this application, because Patent No. 6,410,550 issued after September 24, 1984. Pursuant to 37 C.F.R. §1.775(d)(5)(i) five (5) years are added to the expiration date of Patent No. 6,410,550 (November 13, 2018) giving a date of November 13, 2023. According to 37 C.F.R. §1.775(d)(5)(ii), the dates obtained pursuant to 37 C.F.R. §1.775(d)(5)(i) and 37 C.F.R. §1.775(d)(4) are compared and the earlier date is selected. The date calculated according to 37 C.F.R. §1.775(d)(4) above is May 10, 2020. Therefore, the earlier of these dates is May 10, 2020. Applicant is entitled to an extension of term of Patent No. 6,410,550 until May 10, 2020, *i.e.,* an extension of 545 days from the original expiration date of November 13, 2018.
- 37 C.F.R. §1.775(d)(6) does not apply because Patent No. 6,410,550 issued on June 25, 2002, after September 24, 1984.

(13) Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension of 545 days which is being sought to the term of Patent No. 6,410,550.

(14) The prescribed fee under 37 C.F.R. §1.20(j) for receiving and acting on this application for patent term extension is to be charged to Deposit Account No. 16-1445, as requested in the enclosed transmittal letter.

(15) Please direct all inquiries and correspondence relating to this application for patent term extension as follows:

(16)

A. David Joran
PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

Tel: (212) 733-3381
Fax: (212) 573-1939

Pursuant to 37 C.F.R. §1.740(b), two duplicate copies of these application papers are enclosed herewith. Pursuant to M.P.E.P. §2753 an additional two copies of the application are also enclosed herewith. Accordingly, a total of four copies of the application and one original application for patent term extension of Patent No. 6,410,550 are submitted herewith.

Applicant respectfully requests prompt and favorable action on the merits of this application for extension of the term of Letters Patent No. 6,410,550 of 545 days, based on the regulatory review period for CHANTIX™ (varenicline) Tablets.

Respectfully submitted,
PFIZER INC

Date: June 28, 2006

A. David Joran
Attorney for Applicant
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UNITED STATES PATENT AND TRADEMARK OFFICE

JULY 25, 2002

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Chief Information Officer
Washington, DC 20231
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PFIZER INC
PAUL H. GINSBURG
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NEW YORK, NY 10017-5612

102103870A

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REEL/FRAME: 012920/0128
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
COE, JOTHAM WADSWORTH

DOC DATE: 05/06/2002

ASSIGNOR:
BROOKS, PAIGE ROANNE PALMER

DOC DATE: 05/06/2002

ASSIGNEE:
PFIZER INC.
235 EAST 42ND STREET
NEW YORK, NEW YORK 10017-5755

SERIAL NUMBER: 09402010
PATENT NUMBER: 6410550

FILING DATE: 09/28/1999
ISSUE DATE: 06/25/2002

KIMBERLY WHITE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

05-28-2002

102103870

FORM PTO-1595 (1-31-92) **RECORDATION PAT** — DEPARTMENT OF COMMERCE Patent and Trademark

To the Director – United States Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Jotham Wadsworth Coe
Paige Roanne Palmer Brooks 5-20-02

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Pfizer Inc. MAY 20 2002
Street Address: 235 East 42nd Street
City: New York State: New York Zip: 10017-5755

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____

Execution Date: MAY 6, 2002

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:
A. Patent Application No.(s) B. Patent No. (s)
U.S. Ser. No. 09/402,010

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Paul H. Ginsburg
Internal Address: Pfizer Inc
Street Address: 150 East 42nd Street (150/05/49)
City: New York State: New York ZIP: 10017-5612

6. Total number of pages including cover sheet, attachments and document: 4

7. Total fee (37 CFR 3.41).....$ 40.00

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Signature
MAY 8, 2002 — Date

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CONFORMS WITH FORM PTO-1595

05/24/2002 GTON11 00000130 161445 09402010

ASSIGNMENT

For valuable consideration, the receipt and adequacy of which is hereby acknowledged, we, **Jothan Wadsworth COE and Paige Roanne Palmer BROOKS** of **8 Bush Hill Drive, Niantic, Connecticut 06357, United States of America and 9 Wyassup Road, North Stonington, Connecticut 06359, United States of America** respectively, hereby sell, assign and transfer unto PFIZER INC., a corporation organized and existing under the laws of the State of Delaware, United States of America, and having its principal place of business at 235 East 42nd Street, New York, New York 10017, United States of America, our entire right, title and interest, except as limited hereinbelow, in and to patent application of the United States of America, having PFIZER INC. Docket No. PC 10030A, entitled **ARYL FUSED AZAPOLYCYCLIC COMPOUNDS**; filed in the United States Patent and Trademark Office on **September 28, 1999** and assigned application number **09/402,010**; and our entire right, title and interest, in the United States of America, in and to all our inventions, whether joint or sole, disclosed in said patent application; and our entire right, title and interest in and to all applications filed in the United States of America for Letters Patent for any or all of said inventions; and our entire right, title and interest in and to all Letters Patent granted in the United States of America on the foregoing applications;

and we hereby sell, assign and transfer unto PFIZER PRODUCTS INC., a corporation organized and existing under the laws of the State of Connecticut, United States of America, and having its place of business at Eastern Point Road, Groton, Connecticut 06340, United States of America, our entire right, title and interest, in all countries of the world except the United States of America, in and to all our inventions, whether joint or sole, disclosed in said patent application; and our entire right, title and interest in and to all patent applications filed outside the United States of America for Letters Patent for any or all of said inventions; and our entire right, title and interest in and to all Letters Patent granted outside the United States of America on said patent applications filed outside the United States of America; and the right to claim priority from said patent application under the Paris Convention for the Protection of Industrial Property, and under any and all other such treaties and agreements to which the United

States of America is a party and which afford similar priority-claiming privileges, in all countries of the world except the United States of America;

and we hereby agree, whenever requested, to communicate to said PFIZER INC. and said PFIZER PRODUCTS INC., and their successors and assigns, any facts known to us respecting said inventions, to testify in any legal proceeding respecting said inventions, and to execute all applications or papers necessary to obtain and maintain proper patent protection on said inventions in all countries of the world.

Signed and witnessed this 6th Day of MAY 2002

at **Groton, Connecticut, USA**

Jotham Wadsworth Coe

Jotham Wadsworth COE

In the presence of:

Martin Patrick Allen

Martin Patrick Allen

(Typed or Printed Name of Witness)

Signed and witnessed this 6th Day of MAY 2002

at **Groton, Connecticut, USA**

Paige Roanne Palmer Brooks

Paige Roanne Palmer BROOKS

In the presence of:

Krista Entrop Bianco

Krista Entrop Bianco

(Typed or Printed Name of Witness)

US006410550B1

(12) **United States Patent**
Coe et al.

(10) **Patent No.: US 6,410,550 B1**
(45) **Date of Patent: Jun. 25, 2002**

(54) **ARYL FUSED AZAPOLYCYCLIC COMPOUNDS**

(75) Inventors: **Jotham Wadsworth Coe**, Niantic; **Paige Roanne Palmer Brooks**, North Stonington, both of CT (US)

(73) Assignee: **Pfizer INC**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/402,010**

(22) PCT Filed: **Nov. 13, 1998**

(86) PCT No.: **PCT/IB98/01813**

§ 371 (c)(1),
(2), (4) Date: **Sep. 28, 1999**

(87) PCT Pub. No.: **WO99/35131**

PCT Pub. Date: **Jul. 15, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/070,245, filed on Dec. 31, 1997.

(51) **Int. Cl.**[7] **A61K 31/44**; A61K 31/505; C07D 221/22; C07D 413/00; A61P 1/00

(52) **U.S. Cl.** **514/289**; 514/210.21; 514/228.2; 514/232.8; 514/253.02; 514/253.03; 514/256; 514/281; 514/295; 546/43; 546/74; 546/97; 544/58.2; 544/60; 544/125; 544/126; 544/242; 544/361

(58) **Field of Search** 546/43, 74, 97; 544/58.2, 60, 125, 126, 242, 361; 514/210.21, 228.2, 232.8, 253.02, 253.03, 256, 281, 289, 295

(56) **References Cited**

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Mazzocchi et al., Synthesis and Pharmacological Activity of 2,3,4,5–Tetrahydro1,5 methano–1H–3–benzazepines, Journal of Medicinal Chemistry, vol. 22, No. 4, pp. 455–457, 1979.*

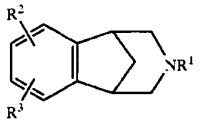
* cited by examiner

Primary Examiner—Brenda Coleman
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Paul H. Ginsburg; Roy F. Waldron

(57) **ABSTRACT**

Compounds of the formula

(I)



and their pharmaceutically acceptable salts, wherein R^1, R^2, and R^3 are defined as in the specification, intermediates in the synthesis of such compounds. pharmaceutical compositions containing such compounds and methods of using such compounds, in the treatment of neurological and psychological disorders.

15 Claims, No Drawings

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

This application is a national stage entry under 35 U.S.C. §371 of PCT/IB98/01813, filed Nov. 13, 1998 which claims the benefit of U.S. Provisional Application Ser. No. 60/070,245, filed Dec. 31, 1997.

BACKGROUND OF THE INVENTION

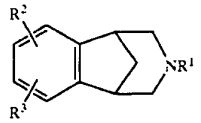
This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac, arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

The compounds of this invention may also be used in combination with an antidepressant such as, for example, a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's Chorea or traumatic brain injury (TBI): in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD, stroke, Huntington's Chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD stroke, Huntington's Chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal antiinflammatory agents and estrogen-like therapy.

Other compounds that bind to neuronal nicotinic receptor sites are referred to in U.S. patent application Ser. No. 08/963,852, which was filed on Nov. 4, 1997 now U.S. Pat. No. 6,020,335. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

This invention relates to aryl fused azapolycyclic compounds of the formula



(I)

R^1 is hydrogen, (C_1-C_6)alkyl, unconjugated (C_3-C_6)alkenyl, benzyl, $XC(=O)R^{13}$ or $—CH_2CH_2—O—(C_1-C_4)$alkyl;

R^2 and R^3 are selected, independently, from hydrogen, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, amino, halo, cyano, $—SO_q(C_1-C_6)$alkyl wherein q is zero, one or two, (C_1-C_6)alkylamino-, $[(C_1-C_6)alkyl]_2amino$-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ $—XC(=O)R^{13}$, aryl-(C_0-C_3)alkyl- or aryl-(C_0-C_3)alkyl-O—, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-(C_0-C_3)alkyl- or heteroaryl-(C_0-C_3)alkyl-O—, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and $X^2(C_0-C_6)$alkoxy-(C_0-C_6)alkyl-, wherein X^2 is absent or X^2 is (C_1-C_6)alkylamino- or $[(C_1-C_6)alkyl]_2amino$-, and wherein the (C_0-C_6)alkoxy-(C_0-C_6)alkyl- moiety of said $X^2(C_0-C_6)$alkoxy-(C_0-C_6)alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said (C_0-C_6)alkoxy-(C_0-C_6)alkyl- moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said (C_0-C_6)alkoxy-(C_0-C_6)alkyl- may be optionally substituted with from two to seven fluonne atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-(C_0-C_3)alkyl- and said heteroaryl-(C_0-C_3)alkyl- may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from (C_1-C_6)alkyl optionally substituted with from one to seven fluonne atoms, (C_1-C_6)alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, cyano, amino, (C_1-C_6)-, $[(C_1-C_6)alkyl]_2amino$-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ and $—XC(=O)R^{13}$;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from (C_0-C_6)alkoxy-(C_0-C_6)alkyl-, wherein the total number of carbon atoms does not

exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, oxo, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1-C_6)alkylamino-, $[(C_1-C_6)alkyl]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, and $-XC(=O)R^{13}$;

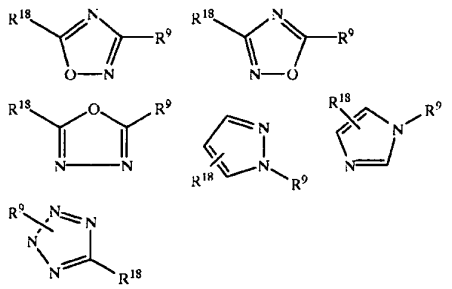
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1-C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, —N—(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1-C_6)alkylene:

with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, and (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen;

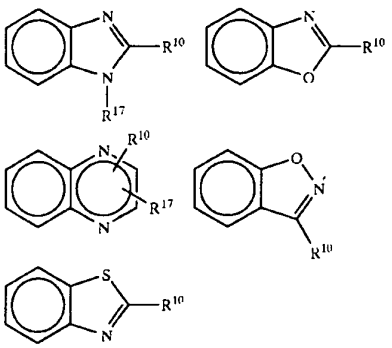
and the pharmaceutically acceptable salts of such compounds.

Examples of heteroaryl groups that each of R^2 and R^3 can be are the following: thienyl, oxazoyl, isoxazolyl, pyridyl, pyrimidyl, thiazolyl, tetrazolyl, isothiazolyl, triazolyl, imidazolyl, tetrazolyl, pyrroyl and the following groups:



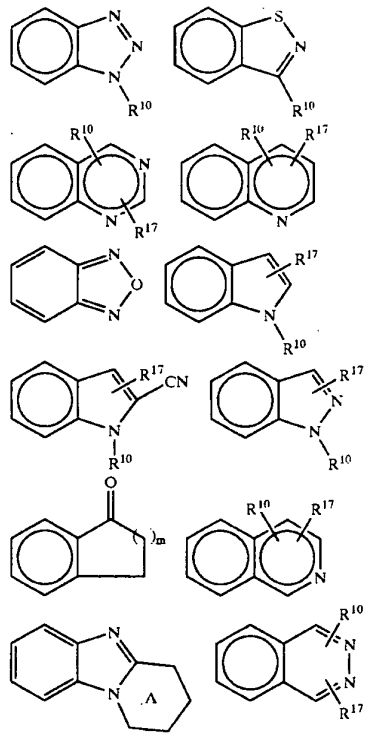
wherein one of R^9 and R^{18} is hydrogen or (C_1-C_6)alkyl, and the other is a bond to the benzo ring of formula I.

Examples of compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:



wherein R^{10} and R^{17} are selected, independently, from (C_0-C_6)alkoxy-(C_0-C_6)alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, (C_1-C_6) alkylamino-, $[(C_1-C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as R^2 and R^3 are defined in the definition of compounds of the formula I above;

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system selected from the following:



wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or $—N(C_1-C_6)$alkyl.

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein neither R^2 nor R^3 is attached to the benzo ring of formula I via an oxygen atom.

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

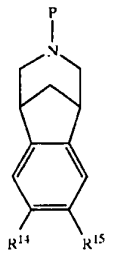
Other embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $—C(=O)R^{13}$, wherein R^{13} is (C_1-C_6)alkyl. Further embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $—C(=O)R^{13}$, wherein R^{13} is (C_1-C_6)alkyl or (C_1-C_3)alkyl optionally substituted with from one to seven fluorine atoms. Other embodiments relate to compounds of the formula I wherein one of R^2 and R^3 is CF_3, fluoro, cyano or C_2F_5.

Other embodiments of this invention relate to compounds of the formula I wherein R^1 is not methyl.

Examples of specific compounds of the formula I are the following:

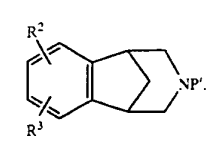
6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3 $1.0^{2,10}.0^{4,8}$] pentadeca-2(10),3,8-triene hydrochloride;
6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$] pentadeca-2(10),3,8-triene hydrochloride;
5,7-dimethyl-6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$] pentadeca-2(10),3,8-triene hydrochloride;
5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2 (10),3,8-triene hydrochloride;
5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2 (10),3,8-triene hydrochloride:
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2 (10),3,8-triene hydrochloride;
4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;
5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene hydrochloride;
5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene hydrochloride.
5-oxa-7-methyl-6-oxo-7,13-diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$] pentadeca-2(10),3,8-triene hydrochloride;
4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene hydrochloride;
4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene hydrochloride;
5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3, 5-triene-4-carbonitrile hydrochloride:
4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene hydrochloride.
6-methyl-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;
7-dimethylamino-5-thia-5-dioxa-6,13-Diazatetracyclo [9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;
6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}.0^{4,9}$] hexadeca-2(11),3,9-triene hydrochloride; and
5,8-dimethyl-6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}.0^{4,9}$]hexadeca-2(11),3,9-triene hydrochloride.

This invention also relates to compounds of the formula



wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1–C_6)$alkyl, allyl, 2,2,2-trichloroethyl or $(C_1–C_6)$alkyl; $—C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; —C(=O)H, $—C(=O)(C_1–C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected, independently, from hydrogen, $(C_1–C_6)$alkyl optionally substituted with from one to seven fluorine atoms; $—C(=O)(C_1–C_6)$alkyl, cyano, hydroxy, nitro, amino, $—O(C_1–C_6)$alkyl or halo: with the proviso that R^{14} and R^{15} can not both be hydrogen when P is hydrogen or methyl. Such compounds are useful as intermediates in the synthesis of compounds of the formula I.

The invention also relates to a compound of the formula



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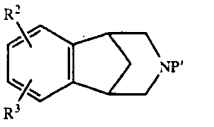


(I')

wherein R^2 and R^3 are defined above; and P' is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or $(C_1–C_6)$alkyl; $—C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in claim 2; —C(=O)H, $—C(=O)(C_1–C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl, or t-butoxycarbonyl (t-Boc).

Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein, includes straight, branched or cyclic, and may include straight and cyclic alkyl moieties as well as branched and cyclic moieties.

The term "alkoxy", as used herein, means "alkyl-O—", wherein "alkyl" is defined as above.

The term "alkylene, as used herein, means an alkyl radical having two available bonding sites (i.e., -alkyl-), wherein "alkyl" is defined as above.

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The compounds of formula I may have optical centers and therefore may occur. in different enantiomeric configurations. The invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula I, as well as racemic and other mixtures thereof.

The present invention also relates to all radiolabeled forms of the compounds of the formula I. Preferred radiolabeled compounds of formula I are those wherein the radiolabels are selected from as ^3H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Such radiolabeled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof,

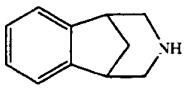
that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear, palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntingon's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

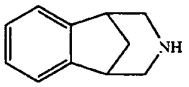
The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI) obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic latera sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI) obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula



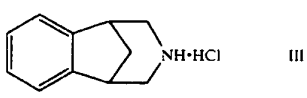
or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

This invention also relates to the pharmaceutically acceptable acid addition salts of the compounds of formula I. Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I are the salts of hydrochlone acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, malate, di-p-toluoyl tartaric acid, and mandelic acid.

DETAILED DESCRIPTION OF THE INVENTION

Except where otherwise stated, R^1 through R^{18}, m and P, and structural formula I in the reaction schemes and discussion that follow are defined as above.

Scheme 1



III

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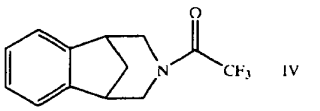

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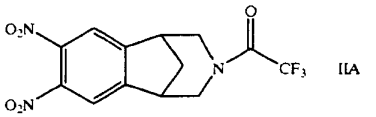
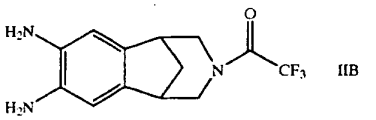
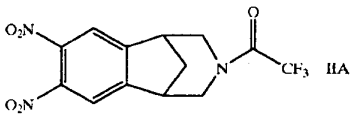


IIA



IIB

Scheme 2



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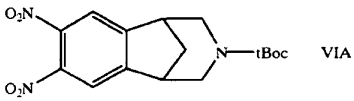

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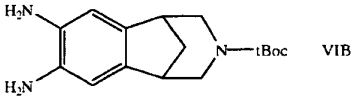

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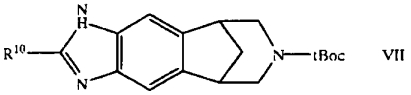
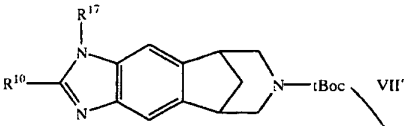


VII



VII'

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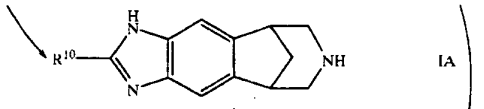

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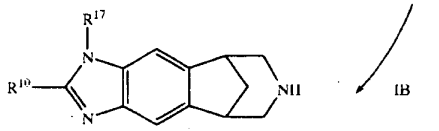

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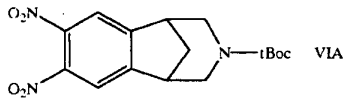
Scheme 3



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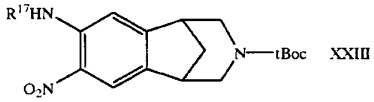

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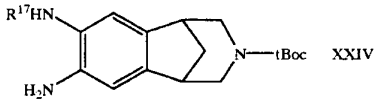

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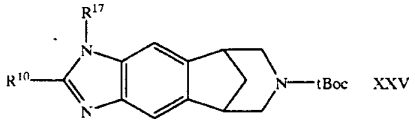
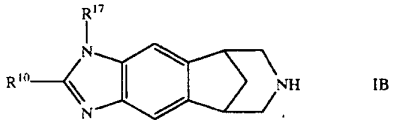


XXV



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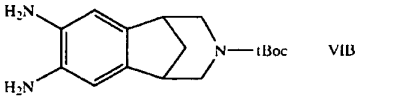
Scheme 4



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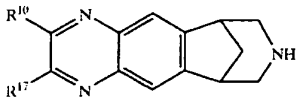

IC

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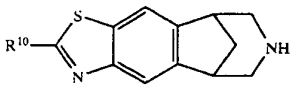
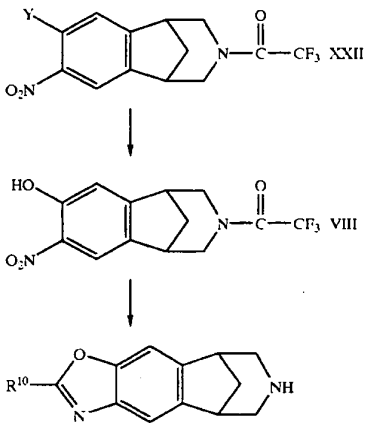


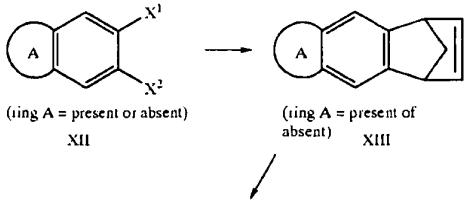
IF

Scheme 5



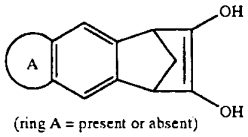
XXII VIII IE

Scheme 7

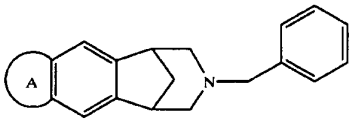


(ring A = present or absent) XII

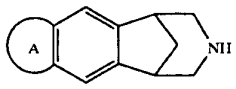
(ring A = present of absent) XIII



(ring A = present or absent) XIIIA

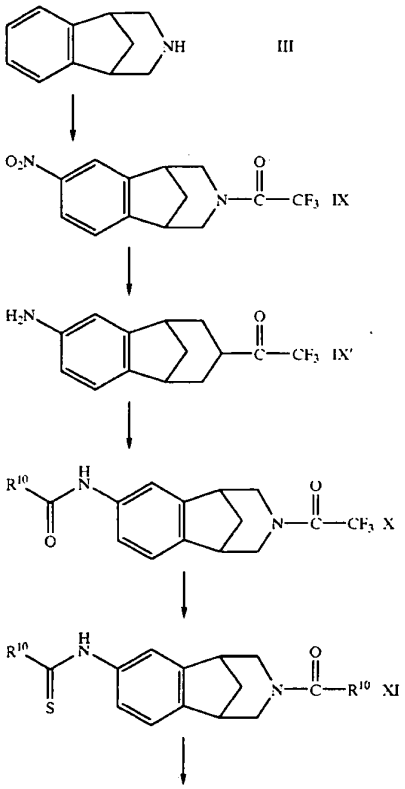


(ring A = present or absent) XIV



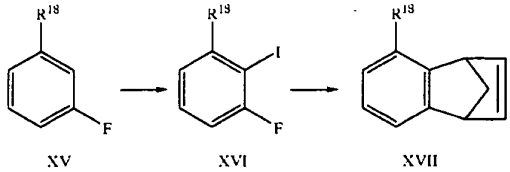
IG: (R^2 and R^3 form ring A)
III: (ring A = absent)

Scheme 6



III IX IX' X XI

Scheme 8



XV XVI XVII

R^{18} = F or C_1-C_6)alkoxy)

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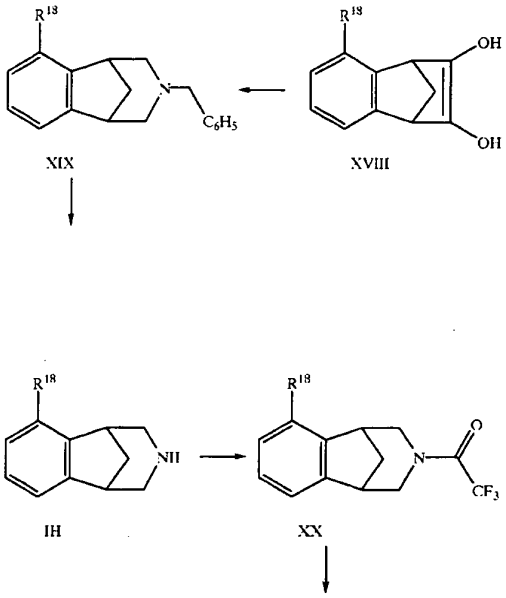
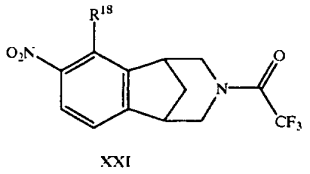
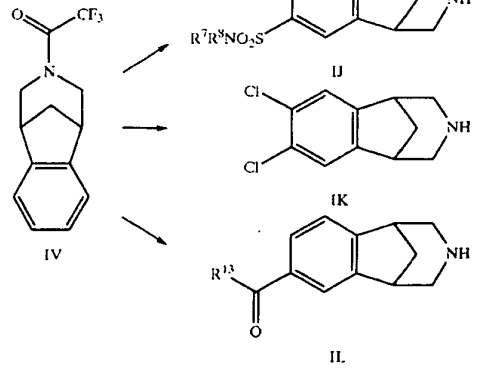
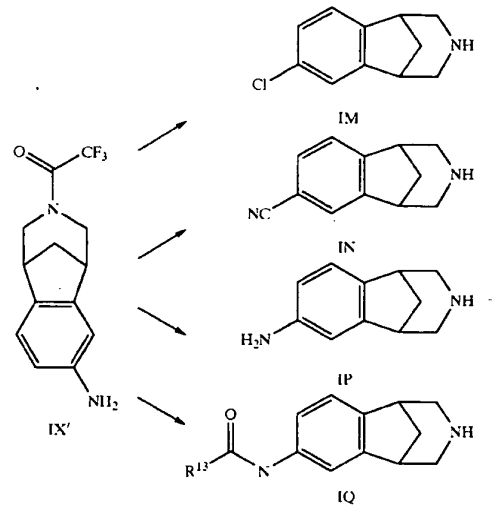




Scheme 9



Scheme 10



Scheme 1–10 illustrate methods of synthesizing compounds of the formula I.

Referring to Scheme 1 the starting material of formula III is reacted with trifluoroacetic anhydride, in the presence of pyridine, to form the compound of formula IV. This reaction is typically conducted in methylene chloride at a temperature from about 0° C. to about room temperature.

The compound of formula IV is then converted into the dinitro derivative of formula IIA by the following process. The compound of the formula IV is added to a mixture of 4 or more equivalents of trifluoromethanesulfonic acid (CF_3SO_2OH) and 2 to 3 equivalents of nitric acid, in a chlorinated hydrocarbon solvent such as chloroform, dichloroethane (DCE) or methylene chloride. The resulting mixture is allowed to react for about 5 to 24 hours. Both of the foregoing reactions are generally conducted at a temperature ranging from about −78° C. to about 0° C. for about 2 hours, and then allowed to warm to room temperature for the remaining time.

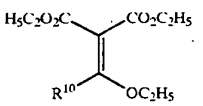
Reduction of the compound of formula IIA, using methods well known to those of skill in the art, yields the compound of formula IIB. This reduction can be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide and running the reaction in methanol at about room temperature.

Referring to Scheme 2, the compound of formula IIA is converted into the corresponding compound wherein the

trifluoroacetyl protecting group is replaced by a t-Boc protecting group (VIA) by reacting it first with an alkali metal or alkaline earth metal (or ammonium) hydroxide or carbonate, and then reacting the isolated product from the foregoing reaction with di-t-butyldicarbonate. The reaction with the alkali or alkaline earth metal (or ammonium) hydroxide or carbonate is generally carried out in an aqueous alcohol, dioxane or tetrahydrofuran (THF) at a temperature from about room temperature to about 70° C., preferably at about 70° C. for about one to about 24 hours. The reaction of the isolated, unprotected amine or an acid addition salt of such amine, from the above reaction with di-t-butyldicarbonate is preferably carried out in a solvent such as THF, dioxane or methylene chloride at a temperature from about 0° C. to about room temperature. This reaction may or may not be conducted in the presence of a base. When the reactant is a salt of the amine, use of a base is preferred. The resulting compound of formula VIA can be converted into the corresponding diamino derivative of formula VIB using the procedure described above for converting the dinitro compound of formula IIA into the corresponding diamino compound of formula IIB.

The conversion of the compound of formula VIB into the desired compound of the formula VII can be accomplished by reacting the compound of formula VIB with a compound of the formula

XXIIA



wherein R^{10} is hydrogen, $(C_1–C_6)$alkyl optionally substituted with from one to seven fluorine atoms, aryl-$(C_0–C_3)$ alkyl wherein said aryl is selected from phenyl and naphthyl, or heteroaryl-$(C_0–C_3)$alkyl wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1–C_6)$alkyl optionally substituted with from one to seven fluorine atoms, $(C_1–C_6)$alkoxy optionally substituted with from one to seven fluorine atoms and cyano. The preferred solvent for this reaction is a 10:1 mixture of ethanol acetic acid. The reaction temperature can range from about 40° C. to about 100° C. It is preferably about 60° C. Other appropriate solvents include acetic acid, ethanol and isopropanol.

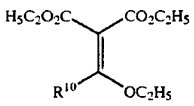
Alternate methods of preparing compounds of the formula VII the compound of formula VIB are described by Segelstein et al., *Tetrahedrón Lett.*, 1993, 34, 1897.

Removal of the t-Boc protecting group from the compound of formula VII yields corresponding compound of formula IA. The protecting group can be removed using methods well known to those of skill in the art. For example, the compound of formula VII can be treated with an anhydrous acid such as hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, preferably hydrochloric acid in ethyl acetate, at a temperature from about 0° C. to about 100° C. preferably from about room temperature to about 70° C. for about one to 24 hours.

The compound of formula VII can be converted into the corresponding compound of formula IB by reacting it with a compound of the formula $R^{17}Z$, wherein R^{17} is defined as R^{10} is defined above, and Z is a leaving group such as a halo or sulfonate (e.g., chloro, bromo, mesylate or tosylate), in the presence of a base such as an alkali metal hydride, hydroxide or carbonate, preferably potassium hydroxide, in a polar solvent such as water, dimethylsulfoxide (DMSO), THF or DMF, preferably a mixture of DMSO and water, and then removing the protecting group as described above. The reaction with $R^{17}Z$ is generally carried out at a temperature from about room temperature to about 100° C., preferably at about 50° C., for about five hours.

Scheme 3 illustrates an alternate method of preparing compounds of the formula IB from the compound of formula VIA. This method is the preferred method of making compounds of the formula IB wherein R^{17} is a bulky group such as an aryl or heteroaryl containing group, or when R^{17} can not be attached, as illustrated in Scheme 2, by alkylation or aryl substitution methods. Referring to Scheme 3, the compound of formula VIA is reacted with the appropriate compound of formula $R^{17}NH_2$ in a polar solvent such as THF, DMF or DMSO, preferably THF, at a temperature from about room temperature to about 100° C., preferably at the reflux temperature, for about four to eighteen hours. The resulting compound of formula XXIII is then converted into the corresponding compound of the formula XXIV by reducing the nitro group to an amino group using methods well known to those of skill in the art. Such methods are referred to above for the conversion of the compounds of the formula IIA into a compound of the formula IIB in Scheme 1, and exemplified in experimental Examples 12B and 18B. Closure of the imidazole ring to form the corresponding compound of formula XXV can then be accomplished by reacting the compound of formula XXIV from the above reaction with a compound of the formula

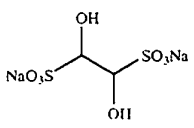
XXIIA



wherein R^{10} is defined as above, as described above for converting compounds of the formula VIB into those of the formula VII.

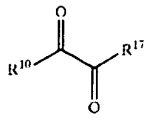
Removal of the protecting group from the compound of formula XXV yields the corresponding compound of formula IB. This can be accomplished using methods well known in the art, for example, as described above for forming compounds of the formula IA from the corresponding compounds of the formula VII.

Scheme 4 illustrates a method of preparing compounds of the formula IC, wherein R^{10} and R^{17} are as defined above. Referring to Scheme 4, the compound of formula VIB is reacted with a compound of the formula



(sodium bisulfite ethane dione addition adduct) in water or another polar solvent such as THF, DMF or DMSO, preferably a mixture of water and a water miscible solvent such as THF, for about one to four hours. The reaction temperature can range from about 40° C. to about 100° C., and is preferably at about the reflux temperature.

Alternatively, the compound of formula VIB can be reacted with a compound of the formula



(double condensation reaction) in a polar solvent such as THF, water, or acetic acid, preferably a mixture of water and THF. This reaction is typically carried out at a temperature from about 40° C. to about 100° C. preferably at the reflux temperature, for about two to four hours.

The desired quinoxoline of formula IC can then be formed by deprotecting the compound formed in either of the foregoing reactions, using the method described above for converting a compound of the formula VII into one of the formula IA.

Scheme 5 illustrates a method of preparing compounds of the formula I wherein R^2 and R^3, together with the benzo ring to which they are attached, form a benzoxazole ring system. Such a compound, wherein R^1 is hydrogen, is depicted in Scheme 5 as chemical formula IE. Referring to Scheme 5, the compound of formula XXII, wherein Y is nitro, halo, trifluoromethanesulfonate or a diazonium salt, is reacted with potassium acetate or another alkali or alkaline earth metal carboxylate in a solvent such as dimethylsulfoxide (DMSO), DMF or acetonitrile, preferably DMSO. This reaction is generally allowed to run for about 12–24 hours. Appropriate reaction temperatures range from about 70° C. to about 140° C. Approximately 100° C. is preferred.

The above reaction yields the compound of formula VIII, which can then be converted into the desired compound having formula IE by the following procedure. First, the compound of formula VIII is reduced by reaction with hydrogen and a palladium or platinum catalyst such as palladium hydroxide in methanol at a temperature from about 0° C. to about 70° C., preferably at about room temperature, to form the corresponding amino derivative. The product of this reaction is then reacted with an acid chloride of the formula $R^{10}COCl$ or an acid anhydride of the formula $(R^{10}CO)_2O$ wherein R^{10} is $(C_1–C_6)$alkyl, or a compound of the formula $R^{10}C(OC_2H_5)_3$, in an appropriate inert solvent such as decalin, chlorobenzene or xylenes. A mixture of xylenes is preferred. This reaction is typically conducted at a temperature from about 120–150° C., preferably at about 140° C. When $R^{10}COCl$ is used as a reactant, it is preferable to add a stoichiometric amount of triethylamine (TEA) or another organic tertiary amine base and a catalytic amount of pyridinium p-toluenesulfonic acid or pyridinium p-toluenesulfonate (PPTs) to the reaction mixture. When $R^{10}C(OC_2H_5)_3$ is used as a reactant, it is preferable to add a catalytic amount of PPTs to the reaction mixture.

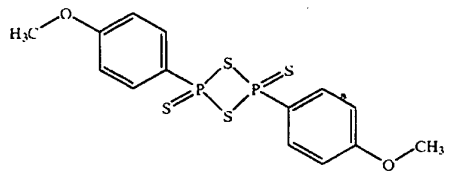
Removal of the trifluoroacetyl nitrogen protecting group yields the desired compound of the formula IE. This can be accomplished using methods well known to those of skill in the art, for example, reacting the protected compound with a lower alkanol and an aqueous alkali or alkaline earth metal (or ammonium) hydroxide or carbonate, aqueous sodium carbonate, at a temperature from about 50° C. to about 100° C., preferably at about 70° C. for about two to six hours.

Scheme 6 illustrates the preparation of compounds of the formula I wherein R^1 is hydrogen and R^2 and R^3, together with the benzo ring to which they are attached, form a benzothiazole ring system. Referring to Scheme 6, the compound of formula III is reacted with trifluoroacetic anhydride to form the corresponding compound wherein the ring nitrogen is protected by a trifluoroacetyl group, and the resulting nitrogen protected compound is then reacted with two equivalents of trifluoromethanesulfonic anhydride and one equivalent of nitric acid to form the corresponding compound of formula IX, wherein there is a single nitro substituent on the benzo ring. The reaction with trifluoroacetic acid is typically conducted in the presence of pyridine. Both of the above reactions are typically conducted in a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, at a temperature from about 0° C. to about room temperature, preferably at about room temperature.

The above transformation can also be accomplished using other nitration methods known to those skill in the art.

Reduction of the nitro group to an amine group can be accomplished as described above to provide a compound of the formula IX'.

The compound of formula IX' is then reacted with a carboxylic acid halide or anhydride of the formula $R^{10}COX$ or $(R^{10}CO)_2O$, wherein X is halo and R^{10} is hydrogen or $(C_1–C_6)$alkyl, and pyridine, TEA or another tertiary amine base, to form a compound of the formula X, which can then be converted to the desired compound having formula XI by reacting it with Lawesson's reagent, which is depicted below



The reaction with $R^{10}COX$, wherein X is halo, or $(R^{10}CO)_2O$ is generally carried out at a temperature from about 0° C. to about room temperature, preferably at about room temperature. The reaction with Lawesson's reagent is generally carried out in a reaction inert solvent such as benzene or toluene, preferably toluene, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature.

Closure to the benzothiazole ring and nitrogen deprotection to form the desired compound of formula IF can be accomplished by reacting the compound of formula XI with potassium ferricyanide and sodium hydroxide in a mixture of water and methanol ($NaOH/H_2O/CH_3OH$), at a temperature from about 50° C. to about 70° C., preferably at about 60° C. for about 1.5 hours.

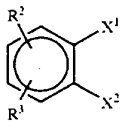
Scheme 7 illustrates a method of preparing the compound of formula III, which is used as the starting material for the process of Scheme 1, or a compound of the formula IG, wherein R^2 and R^3 form a ring (labeled "A" in the Scheme), as defined above in the definition of compounds of the formula I. Referring to Scheme 7, the compound of formula XII, wherein X^1 and X^2 are selected, independently, from chloro, fluoro, bromo and iodo, but where at least one of X^1 and X^2 is Br- or I-, reacted with cyclopentadiene, in the presence of magnesium metal, in a THF, dioxane or other ethereal solvent, at a temperature from about 40° C. to about 100° C., preferably at about the reflux temperature, to form a compound of the formula XIII. Reaction of the resulting compound of formula XIII with N-methylmorpholine-N-oxide (NMO) and osmium tetroxide in acetone at about room temperature yields the corresponding compound of the formula XIIIA.

The compound having formula XIIIA is then converted into the corresponding compound of formula XIV using the following procedure. First, the compound of formula XIIIA is reacted with sodium periodate in a mixture of a chlorinated hydrocarbon, preferably dichloroethane (DCE), and water, or with lead tetraacetate in a chlorinated hydrocarbon solvent, at a temperature from about 0° C. to about room temperature, to generate a dialdehyde or glycal intermediate. The product of this reaction is then reacted with benzylamine and sodium triacetoxyborohydride in a chlorinated hydrocarbon solvent at a temperature from about 0° C. to about room temperature, preferably at about room temperature, to form the desired compound of formula XIV. Removal of the benzyl group from the compound of formula XIV yields the compound of formula III (when ring A is absent) or IG, (when ring A is present). This can be accomplished using methods well known to those of skill in the art, for example, optionally reacting the free base with one equivalent of acid, e.g., hydrochloric acid, (to form the corresponding acid addition salt), followed by hydrogen and palladium hydroxide in methanol at about room temperature.

In the reductive animation step described above and throughout this document, alternatives to benzyl amine, such as ammonia, hydroxylamine, alkoxy amines, methyl amine, allyl amine, and substituted benzyl amines (e.g., diphenylmethyl amine and 2- and 4-alkoxy substituted benzyl amines) can also be used. They can be used as free bases, or as their salts, preferably their acetate salts, and can be subsequently removed by methods described for each by T. W. Greene and G. M. Wuts, "Protective Groups in Organic Synthesis", 1991, John Wiley & Sons, New York, N.Y.

The procedure of Scheme 7 can also be used to prepare compounds of the formula I wherein R^2 and R^3 do not form a ring and are not both hydrogen, by replacing the starting material of formula XII with the appropriate compound having the formula

XII'



Scheme 8, 9 and 10 illustrate methods of preparing compounds of the formula I wherein R^1 is hydrogen: and R^2 and R^3 represent a variety of different substituents, as defined above, but do not form a ring.

Scheme 8 illustrates a variation of the process shown in Scheme 7, which can be used to make a compound identical to that of formula III except that the benzo ring is substituted with a fluoro group or an alkoxy group (R^{18} in Scheme 8). This compound is depicted in Scheme 8 as chemical structure 1H. Referring to Scheme 8, where, for example, R^{18} is F, 1,3-difluorobenzene is reacted with a strong base such as an alkali metal dialkylamine or an alkali metal alkyl (or aryl) in an ethereal solvent such as ethyl ether or THF, at a temperature below −50° C. followed by quenching with iodine or N-iodosuccinamide, to form 1,3-difluoro-2-iodobenzene. The compound 1,3-difluoro-2-iodobenzene (structural formula XVI in Scheme 8) is then converted into the compound of formula IH by a series of reactions (represented in Scheme 8 as XVI→XVII→XVIII→XIX→IH) that are analogous to the series of reactions described above and illustrated in Scheme 7 for converting compounds of the formula XIII into those of the formula IG or III. Conversion of the compound of formula XVI into the compound of formula XVII can also be accomplished by treating a mixture of the compound of formula XVI and cyclopentadiene with an alkyl lithium reagent, preferably n-butyl lithium, in an inert hydrocarbon solvent such as petroleum ether or methyl cyclohexane, at a temperature from about −20° C. to about room temperature, preferably at about 0° C.

The compound of formula IH can then be converted into the corresponding nitrogen protected derivative of formula XX, using the methods described above for synthesizing the compound of formula IV in Scheme 1. Nitration of the compound of formula XX using the method described above for preparing the compound of formula IX in Scheme 6, yields the compound of formula XXI wherein the benzo ring is substituted with both a fluoro and nitro group or an alkoxy group and nitro group. The compound of formula XXI can be used to make a variety of compounds of the formula I wherein one of R^2 and R^3 is fluoro, using methods that are well known to those of skill in the art, for example, by first converting the nitro group to an amino group, converting the amino group to a variety of other substituents, as illustrated in Scheme 10, and then removing the nitrogen protecting group.

The compound of formula XXI acts as a regioisomeric functional equivalent of the compounds having formulas IIA, VIA and XXII, in that the fluorine atom of formula XXI reacts similarly to the nitro and Y groups of formula IIA, VIA, and XXII, and thus can be subjected to the same series of reactions as those described above for the latter three compounds, providing an alternate means for preparing the products of such reactions. Similarly, the alkoxy group of formula XXI (R^{18}=alkoxy) may be converted into a hydroxyl group before or after introduction of the nitro group, and then converted to isomeric products as described above. Also, the trifluoromethanesulfonate salt of such hydroxy derivative can act as a Y-group as described.

Preparation of compounds of formula I where R^2=—O(C_1–C_6)alkyl, (C_1–C_6) alkyl or aryl wherein aryl is defined as above in the definition of formula I, and R^3 is II or one of the other substituents described above in the definition of formula I, can be prepared as described above and illustrated in Scheme 8 by replacing one of the fluorine atoms of the compound of formula XV with —O—(C_1–C_6)alkyl, (C_1–C_6)alkyl or aryl, respectively.

Scheme 9 illustrates methods of preparing compounds of the formula I wherein: (a) R^1 is hydrogen and R^2 is $R^7R^8NO_2S$—: (b) R^1 and R^2 are both chloro: and (c) R^1 is hydrogen and R^2 is $R^{13}C(=O)$—. These compounds are referred to in Scheme 9, respectively, as compounds of formulas IJ, IK and IL.

Referring to Scheme 9, compounds of the formula IJ can be prepared by reacting the compound of formula IV with two or more equivalents of a halosulfonic acid, preferably chlorosulfonic acid, at a temperature from about 0° C. to about room temperature. Reaction of the chlorosulfonic acid derivative so formed with an amine having the formula R^7R^8NH, wherein R^7 and R^8 are defined as above, followed by removal of the nitrogen protecting group, yields the desired compound having formula IJ.

Compounds of the formula IK can be prepared by reacting the compound of formula IV with iodine trichloride in a chlorinated hydrocarbon solvent, followed by removal of the nitrogen protecting group. The reaction with iodine trichloride is typically carried out at a temperature from about 0° C. to about room temperature, and is preferably carried out at about room temperature. In a similar fashion, the analo-

gous mono- or dibrominated or mono- or diiododinated compounds can be prepared by reacting the compound of IV with N-iodosuccinimide or N-bromosuccinimide in a trifluoromethanesulfonic acid solvent, followed by removal of the nitrogen protecting group as described above.

Reaction of the compound of IV with an acid halide of the formula $R^{13}COCl$ or an acid anhydride of the formula $(R^{13}CO)_2O$, with or without a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, in the presence of Lewis acid such as aluminum chloride, at a temperature from about 0° C. to about 100° C., followed by nitrogen deprotection, yields the compound of formula IL. The reaction with the acid halide or anhydride can be carried out using other known Lewis acids or other Friedel-Crafts, acylation methods that are known in the art.

The reactions described herein in which NO_2, $—SO_2NR^7R^8$, $—COR^{13}$, I, Br or Cl are introduced on the compound of formula IV, as depicted in Scheme 9 and described above, can be performed on any analogous compound wherein R^2 is hydrogen, $(C_1–C_6)$alkyl, halo, $(C_1–C_6)$ alkoxy or $—NHCONR^7R^8$, producing compounds of the formula I wherein R^2 and R^3 are defined as in the definition of compounds of the formula I above.

Compounds that are identical to those of the formula IL, but which retain the nitrogen protecting group, can be converted into the corresponding O-acyl substituted compounds, i.e., those wherein the $—C(=O)R^{13}$ group of formula IL is replaced with a $—O—C(=O)R^{13}$ group, using Baeyer-Villiger processes well known to those skilled in the art. The resulting compounds can be partially hydrolyzed, as described in Example 35, to yield the corresponding hydroxy substituted compounds, and then alkylated to form the corresponding alkoxy substituted compounds. Also, as described in Example 36, such O-acyl substituted compounds can be used to prepare variably substituted benzisoxazoles.

Scheme 10 illustrates methods of making compounds of the formula I wherein: (a) R^1 is hydrogen and R^2 is chloro; (b) R^1 is hydrogen and R^2 is cyano; (c) R^1 is hydrogen and R^2 is amino; and (d) R^1 is hydrogen and R^2 is $R^{13}C(=O)N(H)—$. These compounds are referred to in Scheme 10, respectively, as compounds of the formula IM, IN, IP and IQ.

Compounds of formula IM can be prepared from compounds of the formula IX' by generation of a diazonium salt with, for instance, an alkali metal nitrite and strong mineral acid (e.g., hydrochloric acid, sulfuric acid, hydrobromic acid) in water, followed by reaction with a copper halide salt, such as copper (I) chloride. Nitrogen deprotection by the methods described above yields the desired compound of formula IM. Alternative methods for the generation of diazonium salts, as known and practiced by those of skill in the art, can also be used. The foregoing reaction is generally carried out by temperatures ranging from about 0° C. to about 60° C., preferably about 60° C. for about 15 minutes to one hour.

Reaction of the diazodium salt, prepared as described above, with potassium iodide in an aqueous medium provides the analogous iodide derivative. This reaction is generally carried out at a temperature from about 0° C. to about room temperature, preferably at about room temperature. The resulting compound, or its analogous N-tert-butylcarbonate protected form, can be used to prepare the corresponding cyano derivative by reaction with copper (I) cyanide and sodium cyanide in DMF, N,N-dimethylpropylurea (DMPU) or DMSO, preferably DMF, at a temperature from about 50° C. to about 180° C., preferably about 150° C. Nitrogen deprotection as described above provides the desired compound of formula IM.

The above described iodide derivative can also be used to access a variety of other substituents such as aryl, acetylene and vinyl substituents, as well as the corresponding carbonyl esters and amides, by palladium and nickel catalyzed processes known to those of skill in the art, such as Heck, Suzuki and Stille couplings and Heck carbonylations.

Nitrogen deprotection of the compound of formula IX' provides the compound of the formula IP.

The compound of formula IX' can be reacted with a acyl group having the formula $R^{13}COCl$ or $(R^{13}CO)_2O$ using the methods described above, followed by nitrogen deprotection to provide compounds of the formula IQ. In a similar fashion. treatment of the protected amine with a compound having the formula $R^{13}SO_2X$, when X is chloro or bromo, followed by nitrogen deprotection, provides the corresponding sulfonamide derivative.

Other suitable amine protecting groups that can be used, alternatively, in the procedures described throughout this document include $—COCF_3$, $—COCCl_3$, $—COOCH_2CCl_3$, $—COO(C_1–C_6)$alkyl and $—COOCH_2C_6H_5$. These groups are stable under the conditions described herein, and may be removed by methods described for each in Greene's "Protective Groups in Organic Chemistry", referred to above.

In each of the reactions discussed above, or illustrated in Schemes 1–10, above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, with ambient pressure, i.e., about 1 atmosphere, being preferred as a matter of convenience.

The compounds of the formula I and their pharmaceutically acceptable salts (hereafter "the active compounds") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These compounds are, most desirably, administered in dosages ranging from about 0.25 mg up to about 1500 mg per day, preferably from about 0.25 to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.01 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds can be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More particularly, the active compounds can be administered in a wide variety of different dosage forms, e.g., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic

solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc can be used for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar] as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration. a solution of an active compound in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

It is also possible to administer the active compounds topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Biological Assay

The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites is determined by the following procedure which is a modification of the methods of Lippiello, P. M. and Fernandes, K. G. (in *The Binding of L-[^{3}H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes, Molecular Pharm.*, 29, 448–54, (1986)) and Anderson, D. J. and Arnenc, S. P. (in *Nicotinic Receptor Binding of ^{3}H-Cystisine, ^{3}H-Nicotine and ^{3}H-Methylcarnbamylcholine In Rat Brain, European J. Pharm.*, 253, 261–67 (1994)).

Procedure

Male Sprague-Dawley rats (200–300 g) from Charles River were housed in groups in hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.–7 p.m. light period). They received standard Purina Rat Chow and water ad libitum.

The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (*Molec Pharmacol*, 29, 448–454, (1986) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0° in 10 volumes of buffer (w/v) using a Brinkmann Polytron™, setting 6, for 30 seconds. The buffer consisted of 50 mM Tris HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10 minutes; 50,000×g; 0 to 4° C. The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000×g; 0 to 4° C. After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0 g/100 mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$ and has a pH of 74 at room temperature.

Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50 μL of vehicle, blank, or test compound solution, respectively. To each tube was added 200 μL of [^{3}H]-nicotine in assay buffer followed by 750 μL of the membrane suspension. The final concentration of nicotine in each tube was 0.9 nM. The final concentration of cytisine in the blank was 1 μM The vehicle consisted of deionized water containing 30 μL of 1 N acetic acid per 50 mL of water. The test compounds and cytisine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0 to 4° C. in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B™ glass fiber filters using a Brandel™ multi-manifold tissue harvester. Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 m each). The filters were then placed in counting vials and mixed vigorously with 20 ml of Ready Safe™ (Beckman) before quantification of radioactivity. Samples were counted in a LKB Wallach Rackbeta™ liquid scintillation counter at 40–50% efficiency All determinations were in triplicate.

Calculations

Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytisine (B), i.e.,

$$\text{Specific binding}=(C)=(A)-(B).$$

Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e., (E)=(D)–(B).

$$\% \text{ Inhibiton}=(1-((E)/(C)) \text{ times } 100.$$

The compounds of the invention that were tested in the above assay exhibited IC_{50} values of less than 10 μM.

The following experimental examples illustrate, but do not limit the scope of, this invention.

EXAMPLE 1

10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE

A) 1,4-Dihydro-1,4-methano-naphthalene

(Based wholly or in part on a) Wittig, G.; Knauss, E. *Chem. Ber.* 1958, 91, 895. b) Muir, D. J.; Stothers, J. B. *Can. J. Chem.* 1993, 71, 1290.)

Magnesium turnings (36.5 g, 1.5 M) were stirred in anhydrous THF (250 mL) in a dried 2 L 3 neck round bottom flask equipped with a 250 mL non-equalizing addition funnel with a nitrogen (N_2) flow adapter, mechanical stirrer

and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2-Fluorobromobenzene (2 g) was added followed by 1 mL of 3N ethylmagnesium bromide (EtMgBr in THF). The addition funnel was charged with a mixture of cyclopentadiene (94.4 g, 1.43 M. Prepared by the method described in: *Org. Syn.* Col. Vol. V, 414–418) and bromofluorobenzene (250 g, 1.43 M) which was maintained at 0° C. in a separate flask by an ice bath, and transferred to the addition funnel via cannula. Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4×). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation), the heating mantle was removed and the contents of the addition funnel was added dropwise at such rate as to maintain reflux (1.5 hours) The heating mantle was re-applied and a reflux maintained for 1.5 hours. (TLC 100% hexanes R_f0.67).

The reaction was cooled to room temperature and quenched with H_2O (500 mL) and carefully with 1N HCl (200 mL, produces H_2 evolution from unconsumed Mg). To this ~50 mL concentrated HCl was added to dissolve solids. Total addition/quench time ~1 hour. Saturated aqueous sodium chloride (NaCl) solution (300 mL) was added and product hexanes extracted until no potassium permanganate ($KMnO_4$) active product is removed, (4×~250 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (250 mL), sodium bicarbonate Na_2SO_4 dried and concentrated to an oil (~200 g). The product was distilled at 78–83° C. @ 15 mm (131 g, 64%). (An alternative workup is described on p.419 Fieser and Fieser, Vol. I, Reagents for Organic Synthesis, Wiley, N.Y., N.Y.; 1967).

B) 1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol

(Except for the workup method and the quantity of OsO_4 used, based on VanRheenen, V.; Cha. D. Y.; Hartley, W. M. *Org. Syn.* 1988, 6, 342.)

In a 2 L 3 neck round bottom flask equipped with a N_2 flow adapter, mechanical stirrer was placed 1,4-dihydro-1, 4-methano-naphthalene (79.5 g, 560 mmol) stirred in acetone (800 mL) and H_2O (100 mL) and N-methyl morpholine N-oxide (67.5 g, 576 mmol). To this was added osmium tetroxide (OsO_4) (15 mL of a 15 mol % t-BuOH solution, 1.48 mmol. 0.26 mol %) and the mixture was stirred vigorously. After 60 hours, the reaction was filtered, and the white product rinsed with acetone and air dried (60.9 g). The mother liquor was concentrated to an oily solid: acetone trituration, filtration and acetone rinse provided (27.4 g, total 88.3 g, 89%). (TLC 50% EtOAc/hexanes R_f~0.5). mp 176–177.5° C.

C) 10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

(Based on Abdel-Magid, A. F.; Carson, K. G.; Harris. B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* 1996, 61, 3849; and Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* 1979. 22, 455.)

1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol (40 g, 227.3 mmol) was stirred in H_2O (1050 mL) and 1,2-dichloroethane (DCE) (420 mL) in a 2 L round bottom flask under nitrogen with cool water bath (~10° C.). To this sodium periodate ($NaIO_4$) (51 g, 239 mmol) and triethylbenzyl ammonium chloride (Et_3BnNCl) (50 mg) were added. The resulting mixture was stirred for 1 hour (slight initial exotherm), then the layers were separated and the aqueous layer was extracted with DCE (200 mL). The organic layer was washed with H_2O (4×200 mL, or until no reaction to starch iodide is observed in the aqueous wash) then dried through a cotton plug. To this was added benzylamine (25.5 g, 238.6 mmol) and the mixture was stirred for 2 minutes then immediately transferred into the sodium triacetoxyborohydride $NaHB(OAc)_3$/DCE (see below) over 10 minutes.

In a separate 2 L round botton flask flask under nitrogen was magnetically stirred $NaHB(OAc)_3$ (154 g, 0.727 mmol) in DCE (800 mL) at 0° C. (ice bath). To this was added the above mixture over 10 minutes, without delay after the dialdehyde and amine were mixed. The resulting orange mixture was allowed to warm to room temperature and stirred for 30–60 minutes.

The reaction was quenched by addition of saturated sodium carbonate (Na_2CO_3) solution (~300 mL) carefully at first and the mixture was stirred for 1 hour (pH 9). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×300 mL). The organic layer was washed with saturated aqueous NaCl solution (200 mL), dried through a cotton plug, then evaporated to a red oil. This was dissolved in a minimum of Et_2O and filtered through a Silica pad (3×4 inch) eluting with 15% ethyl acetate (EtOAc)/hexanes +1% of 37% aqueous ammonium hydroxide (NH_4OH) solution to remove baseline red color. Concentration affords a light yellow oil (48.5 g, 194.8 mmol, 85.7%). (TLC 10% EtOAC/hexanes R_f0.75). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.16 (m, 7H), 6.89 (m, 2H), 3.48 (m, 2H), 3.08 (m, 2H), 2.80 (d, J=9.5 Hz, 2H), 2.42 (d, J=9.5 Hz, 2H), 2.27 (m, 1H), 1.67 (d, J=10.0 Hz, 1H). APCI MS m/e 250.3 [(M+1)$^+$].

D) 10-Aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene (For an alternative synthesis, see; Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* 1979, 22, 455.)

10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (70.65 g, 284 mmol) was stirred in EtOAc (250 mL) and treated with 3N HCl EtOAc (1.03 eq.) slowly with cooling (ice bath). The resulting precipitate was filtered and rinsed with EtOAc. The solids were dissolved in MeOH (250 mL) in a parr bottle. To this was added $Pd(OH)_2$ (7 g of 20% wt/C) and the mixture was shaken under 50–40 psi of H_2 for 24 hours or until done by TLC. The reaction was filtered through a Celite pad and concentrated to an oily solid. This was azeotroped with methanol (MeOH) (3×) then triturated with acetone, treated with ethyl ether (Et_2O) to precipitate product and filtered. Concentration of the mother liquors and a second treatment provided an off white solid (48.95 g, 251 mmol, 88%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.18 (m, 4H), 2.97 (m, 4H), 2.68 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 1.95 (d, J=11.0 Hz, 1H) APCI MS m/e 160.2 [(M+1)$^+$].

EXAMPLE 2

4-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 6-Fluoro-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* 1976, 98, 753–761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* 1977, 99, 3723–3733.)

Magnesium turnings (0.66 g, 27.2 mmol) were stirred in anhydrous THF (10 mL) in a flame dried 75 mL 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter, magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,5-Difluorobromobenzene (0.1 g) was added followed by of 3N EtMgBr in THF (0.1 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (1.71 g, 25.9 mmol) and 2,5-difluorobromobenzene (5.0 g, 25.9 mmol). Small portions (~0.2 mL) of the intimate mixture

were introduced to assist initiation (~4×). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of the contents of the addition funnel. The reaction was then maintained at reflux for 1 hour.

The reaction was cooled to room temperature and quenched with H_2O (20 mL) followed by aqueous 1N HCl solution (20 mL) to dissolve the solids. Saturated aqueous NaCl solution (30 mL) was added and product was extracted with hexanes (4×25 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil. Chromatography on Silica gel eluting with hexanes provided an oil (780 mg, 19%). (TLC hexanes R_f0.38). ^1H NMR (400 MHz, $CDCl_3$) δ7.10 (m, 1H), 6.97 (d, J=8.0 Hz, 1H), 6.80 (br s, 1H), 6.78 (br s, 1H), 6.59 (m, 1H), 3.87 (br s, 2H) 2.32 (d. J=7.0 Hz, 1H), 2.25 (d, J=7.0 Hz. 1H).

B) 6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

6-Fluoro-1,4-dihydro-1,4-methano-naphthalene (680 mg, 4.22 mmol) and N-methyl morpholine N-oxide (599 mg, 4.43 mmol) were stirred in acetone (50 mL) and H_2O (5 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5% wt. solution in t-BuOH, 0.02 mmol). After 72 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for 1 hour. The florisil was filtered and the filtrate concentrated to produce a crystalline product which was triturated with acetone and filtered (524 mg, 64%) ^1H NMR (400 MHz. $CDCl_3$) δ7.10(dd, J=8.0,5.0 Hz, 1H), 6.90 (dd, J=8.0,2.3 Hz, 1H), 6.75 (ddd, J=8.0,8.0,2.3 Hz, 1H), 3.79 (s, 2H), 3.18 (d, J=1.5 Hz, 2H), 2.22 (d, J=10.0 Hz, 1H), 1.92 (dd, J=10.0,1.5 Hz, 1H). GCMS m/e 194 (M^+).

C) 10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (524 mg, 2.68 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (15 mL) and H_2O (45 mL) then treated with sodium periodate (0.603 mg, 2.82 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2×20 mL). The combined organic layer was washed with H_2O (4×20 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (0.308 mL, 2.82 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0° C.) mixture of $NaHB(OAc)_3$ (1.82 g, 8.58 mmol) in DCE (50 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (520 mg, 80%). (TLC 2% acetone/CH_2Cl_2 R_f 0.40). ^1H NMR (400 MHz, $CDCl_3$) δ7.18 (m, 1H), 6.88 (m, 2H), 3.48 (s, 2H), 3.06 (m, 2H), 2.78 (m, 2H), 2.41 (m, 2H), 2.27 (m, 1H), 1.69 (d, J=10.5 Hz, 1H).

D) 4-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (390 mg, 1.461 mmol), ammonium formate (3.04 g, 48.2 mmol) and 10% $Pd(OH)_2$/C (30 mg) were combined in MeOH (50 mL) and brought to reflux under N_2 for 1.5 hours. Ammonium formate (1.0 g) was added and reflux continued for 0.5 hour. The reaction mixture was filtered through a Celite pad which was rinsed with MeOH. The filtrate was concentrated. The residues were treated with saturated aqueous Na_2CO_3 solution (30 mL) and product extracted with methylene chloride (CH_2Cl_2) (3×25 mL). The organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. The residue was treated with 2N HCl MeOH (5 mL) and concentrated then taken up in minimum of MeOH and saturated with Et_2O. After stirring 18 h. the white crystals were collected by filtration (86 mg, 28%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.27), (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ7.06 (m, 1H), 6.83 (m, 2H), 2.89 (m, 4H), 2.61 (dd, J=12.0 Hz, 2H), 2.37 (m, 1H), 1.87 (d, J=11.5 Hz, 1H). APCI MS m/e 178.2 [(M+1)$^+$]. (HCl salt) mp 260–262° C.

EXAMPLE 3

4-METHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-methylbromobenzene. (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ7.04 (d, J=7.5 Hz, 1H), 6.99 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 2.98–2.90 (m, 4H), 2.63 (m, 2H), 2.35 (m, 1H), 2.32 (s, 3H), 1.87 (d, J=11.5 Hz, 1H). APCI MS m/e 174.2 [(M+1)$^+$]. (HCl salt) mp 254–255° C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.82; N, 5.15.

EXAMPLE 4

4-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G. L., Paradkar. V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall. D. J.; Seibel, W. L.; Reitz, T. J. *J. Org. Chem.* 1983, 48, 2321–2327. Grunewald, G. L.; Markovich. K. M.; Sall. D. J. *J. Med. Chem.* 1987, 30, 2191–2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-trifluoromethylbromobenzene. ^1H NMR (400 MHz, CD_3OD) δ7.71 (s, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H), 3.46 (m, 4H), 3.21 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 2.16 (d, J=11.5 Hz, 1H) APCI MS m/e 228.2 [(M+1)$^+$]. (HCl salt) mp 244–246° C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$; C, 53.44; H, 5.11; N, 5.19. Found C. 53.77; H, 4.82; N, 5.18.

EXAMPLE 5

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (Grunewald. G. L.; Markovich, K. M.; Sall. D. J. *J. Med. Chem.* 1987, 30, 2191–2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^1H NMR (400 MHz, CD_3OD) δ7.65 (s, 2H), 7.52 (m, 1H), 3.65 (br s, 1H), 3.49–3.43 (m, 3H), 3.20 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=1.5 Hz, 1H). APCI MS m/e 228.2 [(M+1)$^+$]. (HCl salt) mp 275–277° C.

EXAMPLE 6

3-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 2,6-Difluoroiodobenzene (Roe, A. M.; Burton, R. A.; Willey, G. L.; Baines. M. W.; Rasmussen, A. C. *J. Med. Chem.* 1968, 11, 814–819. Tamborski, C.; Soloski, E. J. *Org. Chem.* 1966, 31, 746–749. Grunewald, G. L.; Arrington, H. S.; Bartlett, W. J.; Reitz, T. J.; Sall, D. J. *J. Med. Chem.* 1986, 29, 1972–1982.) 1,3-Difluorobenzene (57.05 g, 0.5 M) in THF (75 mL) was added to a −78° C. stirred solution of n-butyllithium (n-BuLi) (200 mL, 2.5 M/hexanes, 0.5 M) and THF (500 mL) under N_2. By controlling the addition rate the internal temperature was maintained below −70° C. The total addition time was ~½ hour. The resulting slurry was stirred an additional ½ hour, then the dispersion was treated with a solution of iodine (126.9 g, 0.5 M) in THF (300 mL) at a rate that maintained an internal temperature below −70° C. After complete addition the mixture was allowed to warm to room temperature, and was treated with H_2O (100 mL) and 10% aqueous $Na_2S_2O_3$ solution (100 mL) and stirred. The layers were separated and the aqueous layer extracted with hexanes (2×250 mL). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (100 mL), H_2O (100 mL), saturated aqueous NaCl solution (100 mL), dried (Na_2SO_4) filtered and concentrated to give a yellow oil (106.5 g). Distillation at ~1–5 mm at ~80° C. provided a light yellow oil (89.5 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.30 (m, 1H), 6.87 (m, 2H) GCMS m/e 240 (M^+).

B) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene

A solution of 2,6-difluoroiodobenzene (5.0 g, 20.8 mmol) and cyclopentadiene (2.07 g, 31.3 mmol) was stirred at 0° C. in P, ether (70 mL, 40–60° C.) under N_2 and treated with n-BuLi (8.74 mL, 2.5M in hexanes, 21.8 mmol) dropwise over 10 minutes. The reaction was quenched after 15 minutes by addition of aqueous 1N HCl solution and the product was extracted with hexanes (3×50 mL). The combined organic layer was washed with H_2O (50 mL), saturated aqueous NaCl solution (50 mL), dried ($MgSO_4$), filtered and evaporated. Chromatography on Silica gel provided product as an oil (1.5 g, 45%) (TLC hexanes R_f0.55). ^{1}H NMR (400 Mhz, $CDCl_3$) δ7.08 (ddd, J=7.0,1.0,0.8 Hz, 1H), 6.96 (ddd, J=8.5,8.3,7.0 Hz, 1H), 6.86 (br s, 2H), 6.72 (ddd, J=8.5,8.3, 0.8 Hz, 1H), 4.25 (br s, 1H), 3.98 (br s, 1H), 2.36 (ddd, J=7.2,1.7,1.7 Hz, 1H), 2.30 (ddd, J=7.2,1.7,1.5 Hz, 1H), GCMS m/e 160 (M^+).

C) 3-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

The title compound was prepared by the methods described in Example 2B,C,D starting with 5-fluoro-1,4-dihydro-1,4-methano-naphthalene. ^{1}H NMR (400 Mhz, CD_3OD) δ7.36 (ddd, J=8.3,7.3,5.0 Hz, 1H), 7.21 (d, J=7.3 Hz, 1H), 7.07 (t, J=8.3 Hz, 1H), 3.62 (br s, 1H), 3.42–3.30 (m, 3H), 3.21 (m, 2H), 2.38 (m, 1H), 2.12 (d, J=11.5 Hz, 1H). APCI MS m/e 178.4[$(M+1)^+$]. mp 269–271° C.

EXAMPLE 7

4-NITRO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride salt (12.4 g, 63.9 mmol) was stirred in CH_2Cl_2 (200 mL). This was cooled (ice bath) and treated with pyridine (12.65 g 160 mmol) followed by trifluoroacetic anhydride (TFAA) (16.8 g, 11.3 mL, 80 mmol) from an addition funnel over 10 minutes. After ~3 hours, the solution was poured into 0.5N aqueous HCl (200 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layer was washed with 0.5N aqueous HCl (50 mL), H_2O (2×50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL)). This solution was dried through a cotton plug, then diluted with ~3% EtOAc and filtered through a 2 inch Silica pad eluted with ~3% EtOAc/CH_2Cl_2. Concentration afforded a clear oil which crystallized to give white needles (15.35 g, 60.2 mmol, 94%). (TLC 30% EtOAc/hexanes R_f0.53). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.18 (m, 4H), 4.29 (br d, J=12.6 Hz, 1H), 3.84 (br d, J=12.6 Hz, 1H), 3.51 (dd, J=12.6,1.5 Hz, 1H), 3.21 (br s. 1H), 3.10 (br s, 1H), 3.10 (br d, J=12.6 Hz, 1H), 2.37 (m, 1H), 1.92 (d, J=10.8 Hz, 1H). GCMS m/e 255 (M^+). mp 67–68° C.

B) 1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone (Based on the method described by Coon, C. L., Blucher. W. G.; Hill, M. E. *J. Org. Chem.* 1973, 25, 4243.)

To a solution of trifluoromethanesulfonic acid (2.4 ml, 13.7 mmol) in CH_2Cl_2 (10 ml) stirred at 0° C. was slowly added nitric acid (0.58 ml, 27.4 mmol) generating a white precipitate. After 10 minutes the resulting mixture was cooled to −78° C. and treated with 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-yl)-2,2,2-trifluoro-ethane (3.5 g, 13,7 mmol) in CH_2Cl_2 (15 ml) dropwise from an addition funnel over 5 minutes. The reaction was stirred at −78° C. for 30 minutes then warmed to 0° C. for 1 hour. The reaction mixture was poured into a vigorously stirred ice (100 g) The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×30 ml). The organic layer was combined and washed with H_2O (3×30 ml). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (20 mL) and H_2O (20 mL) then dried through a cotton plug and concentrated to give an orange oil that solidified on standing (4.2 g). Chromatography yielded pure product as a crystalline solid (3.2 g, 78%). (TLC 30% EtOAc/hexanes R_f0.23). ^{1}H NMR (400 MHz, $CDCl_3$) δ8.12 (br d, J=8.0 Hz, 1H), 8.08 (br s, 1H), 7.37 (br d, J=8.0 Hz, 1H), 4.38 (br d, J=12.6 Hz, 1H), 3.94 (br d, J=12.6 Hz, 1H), 3.59 (br d, J=12.6 Hz, 1H), 3.43–3.35 (m, 2H), 3.18 (br d, J=12.6 Hz, 1H), 2.48 (m, 1H), 2.07 (d, J=10.8 Hz, 1H). GCMS m/e 300 (M^+).

C) 4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (182 mg, 0.61 mmol) was stirred with Na_2CO_3 (160 mg, 1.21 mmol) in MeOH (3 mL) and H_2O (1 mL) at 70° C. for 18 hours. The mixture was concentrated, water was added and the product was extracted with CH_2Cl_2. The organic layer was extracted with 1N aqueous HCl (3×20 mL) and the acidic layer washed with CH_2Cl_2 (2×20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3(s) and product was extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried through a cotton plug and concentrated to an oil. This was dissolved in MeOH and treated with 1N HCl MeOH, concentrated to solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (73 mg, 50%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.38). ^{1}H NMR (400 MHz, DMSO-d_6) δ8.21 (s, 1H), 8.18 (dd, J=8.0,2.0 Hz. 1H), 7.59 (d, J=8.0 Hz, 1H), 3.43 (br s, 2H), 3.28 (m, 2H), 3.07 (dd, J=13.0, 13.0 Hz, 2H), 2.24 (m, 1H), 2.08 (d, J=11.5 Hz, 1H). APCI MS m/e 205.1 [$(M+1)^+$] mp 265–270° C.

EXAMPLE 8

4-AMINO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (500 mg, 2.08 mmol) was stirred in 1,4-dioxane (40 mL) and treated with saturated aqueous Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (1.8 g, 8.31 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4×30 mL), dried through a cotton plug and concentrated to provide an oil (500 mg, 91%).

This oil (500 mg, 1.64 mmol) was dissolved in MeOH (30 mL), treated with 10% Pd/C (~50 mg) and hydrogenated under a H_2 atmosphere (45 psi) for 1 hour. The mixture was filtered through a Celite pad and concentrated to a clear oil (397 mg, 88%)

This oil (50 mg, 0.18 mmol) was stirred in 3N HCl EtOAc (3 mL) for 2 hours then concentrated to a white solid (25 mg, 56%). ^{1}H NMR (400 Mhz, DMSO-d_6) δ7.38–7.10 (3H), 3.60 (br s, 2H), 3.25 (m, 2H), 2.98 (m, 2H), 2.18 (m, 1H), 1.98 (d, J=11.5 Hz, 1H). APCI MS m/e 175.1 [(M+1)$^+$] mp 189–192° C.

EXAMPLE 9

N^1-[10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN4-YL]ACETAMIDE HYDROCHLORIDE

A) 1-(4-Amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone

Hydrogenation of 1-(4-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)2.2.2-trifluoro-ethanone (2.0 g, 6.66 mmol) under a H_2 atmosphere (40 psi) and 10% Pd/C (200 mg) in MeOH over 1.5 hours, filtration through Celite and concentration affords a yellow oil (1.7 g). TLC 50% EtOAc/hexanes R_f0.27). ^{1}H NMR (400 MHz, $CDCl_3$) δ6.99 (m, 1H), 6.64 (br s, 1H), 6.57 (m, 1H), 4.25 (m, 1H), 3.82 (m, 1H), 3.50 (m, 1H), 3.17–3.07 (m, 3H), 2.35 (m, 1H), 1.90 (d, J=10.8 Hz, 1H). GCMS m/e 270 (M$^+$).

B) N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-acetamide

1-(4-Amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone (850 mg, 3.14 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with triethyl amine (0.53 mL, 3.76 mmol) and acetyl chloride (0.23 mL, 3.2 mmol) then stirred 18 hours. Standard $NaHCO_3$ workup yielded an oil which was chromatographed to provide a clear oil (850 mg, 87%). (50% EtOAc/hexanes R_f0.28).

C) N^1-[10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien4-yl]acetamide hydrochloride

N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien4-yl)-acetamide (100 mg, 0.32 mmol) was stirred with Na_2CO_3 (70 mg, 0.64 mmol) in MeOH (10 mL) and H_2O (2 mL) at 70° C. for 18 hours. The mixture was concentrated, water was added and the product was extracted with EtOAc. The organic layer was extracted with 1N aqueous HCl (3×20 mL) and the acidic layer washed with EtOAc (2×20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3 (s) and product was extracted with EtOAc (3×20 mL). The organic layer was dried (sodium sulfate (Na_2SO_4)) and concentrated to an oil. This material was dissolved in MeOH and treated with 3N HCl EtOAc (3 mL), concentrated and recrystallized from MeOH/Et_2O to provide a solid (40 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ9.98 (s, 1H), 9.02 (br m, NH), 7.65 (s, 1H), 7.55 (br s, NH), 7.36 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 3.33 (m, 4H), 2.96 (m, 2H), 2.13 (m, 1H), 2.00 (s, 3H), 1.96 (d, J=10.5 Hz, 1H). APCI MS m/e 217.2 [(M+1)$^+$]. mp 225–230° C.

EXAMPLE 10

6-METHYL-5-THIA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) N-(10-Trifluorothioacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)thioacetamide

N-(10-Trifluoroacetyl-10-aza-tricyclo[6 3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-thioacetamide (850 mg, 2.72 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (1.1 g, 2.72 mmol) were combined in toluene (10 mL) and brought to reflux for 1.5 hours. After cooling the reaction was worked up with EtOAC/saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to produce product (410 mg, 44%). (50% EtOAc/hexanes R_f 0.38)

B) 6-Methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

The above oil, 2,2,2-trifluoro-N-(10-trifluorothioacetyl-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-thioacetamide, (360 mg, 1.05 mmol) was dissolved in MeOH (10 mL) and 1N NaOH (5 mL) and added to potassium ferricyanide ($K_3Fe(CN)_6$)(1.72 g, 5.23 mmol) in H_2O (10 mL). This mixture was warmed to 60° C. for 1.5 hours, cooled, concentrated and worked up with EtOAc/H_2O. This material was stirred in dioxane (20 mL) and treated with H_2O (50 mL)) and Na_2CO_3 to achieve pH 10. To this was added di-t-butyldicarbonate (436 mg, 2.0 mmol) and the mixture was stirred for 18 hours. The reaction was concentrated, treated with H_2O and extracted with CH_2Cl_2. The product was chromatographed (Silica 30% EtOAc/hexanes R_f0.41) to yield an oil (100 mg).

The above product was treated with 3N HCl/EtOAc (3 mL) and warmed to reflux for ~15 minutes then concentrated to a solid which was azeotroped with CH_2Cl_2 (2×). These solids were dissolved in a minimum amount of MeOH then saturated with Et_2O and stirred, The resulting white crystalline powder was collected by filtration (40 mg, 14%).

^{1}H NMR (400 MHz, DMSO-d_6) δ9.46 (s, NH), 7.65 (s, 1H), 7.82 (s, 1H), 7.65 (br m, NH), 3.36 (m, 2H), 3.24 (m, 2H), 3.02 (m, 2H), 2.76 (s, 3H), 2.23 (m, 1H), 2.06 (d, J=10.8 Hz, 1H). APCI MS m/e 231.1 [(M+1)$^+$] mp 183–184° C.

EXAMPLE 11

4,5-DINITRO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE

A) 1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoroethanone (Based on the method described in Coon, C. L.; Blucher. W. G.; Hill, M. E. *J. Org. Chem.* 1973, 25, 4243. For an additional related example of dinitration see: Tanida, H.; Ishitobi, H.; Irie, T.; Tsushima, T. *J. Am. Chem. Soc.* 1969, 91, 4512.)

To a solution of trifluoromethanesulfonic acid (79.8 ml, 902.1 mmol) in CH_2Cl_2 (550 ml) stirred at 0° C. was slowly added nitric acid (19.1 ml, 450.9 mmol) generating a white precipitate. After 10 minutes, 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (50 g, 196 mmol) in CH_2Cl_2 (300 ml) was added dropwise from an addition funnel over 30 minutes. The reaction was stirred at 0° C. for 2.5 hours and then stirred at room temperature for 24 hours. The reaction mixture was poured into a vigorously stirred mixture of H_2O (500 ml) and ice (400 g). The layers were separated and the aqueous layer back extracted with CH_2Cl_2 (3×300 ml). The organic layer was combined and

washed with H_2O (3×300 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (2×100 ml). The organic layer was combined and washed with saturated aqueous $NaHCO_3$ solution (200 mL) and H_2O (200 mL) then dried through a cotton plug and concentrated to solids. Trituration with EtOAc/hexanes produced off white solids which were filtered and dried (52 g, 151 mmol, 77%. The mother liquor was chromatographed to give an additional 4.0 g for a total of 56.0 g (82.8%). (TLC 50% EtOAc/hexanes R_f0.29) ^1H NMR (400 MHz, $CDCl_3$) δ7.77 (s, 1H), 7.75 (s, 1H), 4.39 (br d, J=13.0 Hz, 1H), 3.98 (br d, J=13.0 Hz, 1H), 3.65 (d, J=13.0 Hz, 1H), 3.49 (br s, 1H), 3.44 (br s, 1H), 3.24 (br d, J=12.6 Hz, 1H), 2.53 (m, 1), 2.14 (d, J=11.5 Hz, 1H). GCMS m/e 345 (M^+).

B) 4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-triflouroethanone (3.7 g, 10.7 mmol) and Na_2CO_3 (2.3 g, 21.4 mmol) were combined in MeOH (50 mL)) and H_2O (20 mL) then warmed to reflux for 18 hours. The reaction was cooled, concentrated, treated with H_2O and extracted with CH_2Cl_2 (3×50 mL) then dried through a cotton plug. After concentration. the residue was chromatographed to provide brown solids. (1.9 g. 71%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.36). ^1H NMR (400 MHz, $CDCl_3$) δ7.69 (s, 2H), 3.17 (br s, 2H), 3.11 (d, J=12.6 Hz, 2H), 2.53 (m, 1H), 2.07 (d, J=11.0 Hz, 1H). GCMS m/e 249 (M^+).

EXAMPLE 12

6-METHYL-7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene, (1.9 g, 7.6 mmol) was stirred in 1,4-dioxane (75 mL) and treated with saturated aqueous Na_2CO_3 solution (10 mL). To this was added di-t-butyldicarbonate (3.31 g, 15.2 mmol). After stirring 6 hours the reaction was treated with H_2O (50 mL) and extracted with EtOAc (4×25 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide product (1.9 g, 71%). (TLC 30% EtOAc/hexanes (NH_3) R_f0.58). ^1H NMR (400 MHz, $CDCl_3$) δ7.77 (br s, 1H), 7.72 (br s, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 3.39 (br s, 1H), 3.27 (br s, 1H), 3.25 (m, 1H), 3.18 (m, 1H), 2.46 (m, 1H), 2.02 (d, J=11.0 Hz, 1H).

B) 4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7) 3,5-triene-10-carboxylic acid tert-butyl ester (1.9 g, 5.44 mmol) was hydrogenated in MeOH under a H_2 atmosphere (45 psi) over 10% Pd/C (100 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (1.5 7 g, 100%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.14).

C) 6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see: Segelstein, B. E.; Chenard, B. L.; Macor, J. E.; Post, R. J. *Tetrahedron Lett.* 1993, 34, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (700 mg, 2.42 mmol) was dissolved in EtOH (10 mL) and acetic acid (HOAc) (1 mL) and treated with 1-ethoxyethylenemalononitrile (329 mg, 2.42 mmol). The resulting mixture was warmed to 60° C. and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3×50 mL), then dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide brown solids (247 mg, 36%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.28).

D) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Pilarski, B. *Liebigs Ann. Chem.* 1983, 1078.)

6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (80 mg, 0.267 mmol) was stirred in 50% aqueous NaOH solution (3 mL) and DMSO (1 mL) then treated with 1-iodopropane (0.03 mL, 0.321 mmol). This mixture was warmed to 40° C. for 2 hours then cooled, treated with H_2O and extracted with EtOAc. The organic layer was washed with H_2O (3×) then dried (Na_2SO_4), filtered and concentrated to an oil (90 mg,.0.253 mmol). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.15).

E) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,10}$]pentadeca-2(10),3.5.8-tetrane-13-carboxylic acid tert-butyl ester (90 mg, 0.253 mmol) was dissolved in 3N HCl EtOAc (5 mL) and warmed to 100° C. for ½ hour. The mixture was cooled, concentrated, slurried in EtOAc, and filtered to provide a white solid (25 mg, 34%). ^1H NMR (400 MHz, DMSO-d_6) δ9.56 (s, NH), 7.91 (s, 1H), 7.83 (br m, NH), 7.74 (s, 1H), 4.38 (m, 2H), 3.48 (m, 2H), 3.32 (m, 2H), 3.10 (m, 2H), 2.87 (s, 3H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H) 1.85 (m, 2H). 0.97 (m, 3H). mp 147–150° C.

EXAMPLE 13

5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Segelstein, B. E.; Chenard, B. L.; Macor, J. E.; Post. R. J. *Tetrahedron Lett.* 1993, 34, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (1.0 g, 3.45 mmol) was dissolved in EtOH (10 mL) and HOAc (1 mL) and treated with ethoxymethylenemalononitrile (421 mg, 3.45 mmol). The resulting mixture was warmed to 60° C. and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3×50 mL), then dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide brown solids (580 mg, 56%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.28)

B) 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^1H NMR (400 MHz, D_2O) δ8.95 (s, 1H), 7.67 (s, 2H), 3.45 (br s, 2H), 3.31 (d, J=12.5 Hz, 2H), 3.13 (d, J=12.5 Hz, 2H), 2.30 (m, 1H), 1.99 (d, J=11.5 Hz, 1H). APCI MS m/e 200.1 [(M+1)$^+$]. mp>250° C.

EXAMPLE 14

7-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, D_2O) δ8.97 (s, 1H), 7.71 (s, 1H), 7.67 (s, 1H), 3.94 (s, 3H), 3.48 (m, 2H), 3.33 (d, J=12.2 Hz, 2H), 3.14 (d, J=12.2 Hz, 2H), 2.34 (m, 1H), 2.03 (d, J=11.5 Hz, 1H). APCI MS m/e 214.2 [(M+1)$^+$].

EXAMPLE 15

6-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.40 (br m, NH), 7.77 (br m, NH), 7.70 (s, 1H), 3.44 (m, 2H), 3.30 (m, 2H), 3.05 (br d, J=11.0 Hz, 2H), 2.79 (s, 3H), 2.23 (m, 1H), 2.10 (d, J=10.8 Hz, 1H). GCMS m/e 213.5 (M$^+$).

EXAMPLE 16

6,7-DIMETHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.52 (s, NH), 7.84 (s, 1H), 7.82 (br m, NH), 7.72 (s, 1H), 3.90 (s, 3H), 3.45 (m, 2H), 3.28 (m, 2H), 3.04 (m, 2H), 2.82 (s, 3H), 2.23 (m, 1H), 2.12 (d, J=11.0 Hz, 1H). APCI MS m/e 228.2 [(M+1)$^+$]. mp 225–230° C.

EXAMPLE 17

7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1$0^{2,10}$.$0^{4,8}$]pentadeca-2(10)3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodopropane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.52 (s, 1H), 9.45 (br s, NH), 7.97 (s, 1H), 7.85 (s, 1H), 7.83 (br m, NH), 4.43 (m, 2H), 3.49 (m, 2H), 3.33 (m, 2H), 3.08 (m, 2H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.92 (m, 2H), 0.93 (m, 3H). APCI MS m/e 242.2[(M+1)$^+$]. mp 170–171° C. (subl.).

EXAMPLE 18

7-BUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5,8-triene-10-carboxylic acid tert-butyl ester (For conditions, see; Senskey, M. D.; Bradshaw, J. D.; Tessier, C. A.; Youngs, W. J. *Tetrahedron Lett.* 1995, 36, 6217.)

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (500 mg, 1.43 mmol) and 1-butylamine (1.42 mL, 14.3 mmol) were combined in THF (5 mL) and stirred 4 hours. The mixture was diluted with EtOAc (50 mL)) and washed with H_2O (3x30 mL) then dried (Na_2SO_4), filtered and concentrated to an oil. This oil was passed through a Silica gel filter column to remove baseline impurities eluting with 30% EtOAc/hexanes (510 mg, 1.41 mmol, 99%).

B) 4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (460 mg, 1.27 mmol) was treated with ammonium formate (850 mg, 12.7 mmol) and 10% $Pd(OH)_2$/C (50 mg) in MeOH (20 mL) and brought to reflux for 1 hour then filtered through a Celite pad and concentrated. The solids were treated with saturated aqueous Na_2CO_3 solution, extracted with CH_2Cl_2 (3x30 mL) and dried by filtration through a cotton plug to give an oil (440 mg, 100%).

C) 7-Butyl-5,7,13-triazatetracyclo[9.3.$1^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (440 mg, 1.27 mmol) was dissolved in EtOH (20 mL) and HOAc (3 mL) and treated with ethoxymethylenemalononitrile (186 mg, 1.52 mmol). The resulting mixture was warmed to 60° C. and stirred 18 hours. The reaction was cooled, concentrated, treated with H_2O and saturated aqueous Na_2CO_3 solution then extracted with EtOAc (3x50 mL) and dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide a yellow oil. (400 mg, 89%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.70).

D) 7-Butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

7-Butyl-5,7,13-triazatetracyclo[9.3.$1^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.93 (brs, NH), 9.68 (s, 1H), 7.99 (s, 1H), 7.92 (br m, NH), 7.87 (s, 1H), 4.50 (m, 2H), 3.49 (m, 2H), 3.30 (m, 2H), 3.08 (m, 2H), 2.26 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.88 (m, 2H), 1.32 (m, 2H), 0.82 (t, J=7.0 Hz, 3H). APCI MS m/e 256.2 [(M+1)$^+$]. mp 204–208° C.

EXAMPLE 19

7-Isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and isobutylamine were converted to the title compound utilizing the methods described in Example 18A–D. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.74 (s, 1H), 7.52 (s, 1H), 7.14 (s, 1H), 3.90 (dd, J=7.5,2.0 Hz, 2H), 3.04–2.97 (m, 4H), 2.70 (dd, J=12,8.2,3 Hz, 2H) 2.42 (m, 1H), 2.19 (m, 1H), 1.98 (d, J=10.5 Hz, 1H), 0.93 (m, 6H). APCI MS m/e 256.2 [(M+1)$^+$]. mp 147–150° C. (subl.).

EXAMPLE 20

6-METHYL-7-ISOBUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Amino-5-isobutylamino-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (250 mg, 0.74 mmol) from Example 19B was dissolved in EtOH (10 mL) and HOAC (3 mL) and treated with 1-ethoxyethylenemalononitrile (118 mg, 0.87 mmol). The reaction proceeded as in Example 18C (18 h) and was worked up similarly to provide product (TLC 3% MeOH/CH_2Cl_2 (NH_3) R_f0.57).

B) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. APCI MS m/e 270.3 [$(M+1)^+$]. mp 129–130° C. (subl.).

EXAMPLE 21

7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A. 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were converted to 4-phenylamino-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl at 75° C. for 4 hours in the coupling step. This was then converted to the title compound utilizing the methods described in Example 18B,C,D. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.08 (1H), 7.78–7.57 (m, 7H), 3.47–3.00 (m, 6H), 2.23 (m, 1H), 2.09 (d, J=11.5 Hz, 1H). APCI MS m/e 276.2 [$(M+1)^+$]. mp 210–213° C.

EXAMPLE 22

6-METHYL-7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.$10^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 21 and Example 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were converted to the, title compound, ^{1}H NMR (400 MHz, DMSO-d_6) δ7.79 (s, 1H), 7.73–7.56 (m, 5H), 7.32 (s, 1H), 3.46–2.99 (m, 6H), 2.66 (s. 3H), 2.23 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). APCI MS m/e 290.2 [$(M+1)^+$]. mp>250° C.

EXAMPLE 23

7-NEOPENTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A–D, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound, t-Boc precursor GCMS m/e 369 (M^+). (HCl salt) mp>250° C.

EXAMPLE 24

6-METHYL-7-NEOPENTYL-5,7,13-TRIAZATETRACYCLCO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10)3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example, 21 and 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound. ^{1}H NMR (400 MHz DMSO-d_6) δ7.31 (s, 1H), 7.27 (s, 1H), 7.02 (br s, NH), 4.41 (t, J=13.0 Hz, 2H), 3.90 (s, 3H), 3.47–3.26 (m, 6H), 2.20 (m, 1H), 2.00 (d, J=11.5 Hz, 1H), 0.90 (s, 9H), t-Boc precursor APCI MS m/e 384.2 [$(M+1)^+$]. mp>250° C.

EXAMPLE 25

6,7-DIMETHYL-5,8,14-TRIAZATETRACYCLO[10.3.$10^{2,11}$.$0^{4,9}$]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE (Based on the following procedure: Jones. R. G.; McLaughlin, K. C. *Org. Syn.* 1963, 4, 824, b) Ehrlich. J., Bobert. M. T. *J. Org. Chem.* 1947, 522.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (100 mg, 0.35 mmol) was warmed to 80° C. in H_2O (5 mL). To this butane 2,3-dione (0.034 mL, 0.38 mmol) was added under N_2 for 2 hours. The reaction was cooled to room temperature and extracted with EtOAc (3×40 ml). The combined organic layer was washed with H_2O (2×30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an oil (120 mg, 100%). The oil was dissolved in 2N HCl MeOH (5 mL) and warmed to reflux for 30 minutes, then concentrated. Recrystallization from MeOH/Et_2O provided a white powder (50 mg, 43%). (TLC EtOAc R_f0.14). ^{1}H NMR (400 MHz, DMSO-d_6) δ7.85 (s, 2H), 3.50 (br s, 2H), 3.32 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.64 (s, 6H), 2.24 (m, 1H), 2.13 (d, J=11.0 Hz, 1H). t-Boc precursor APCI MS m/e 340.3 [$(M+1)^+$].

EXAMPLE 26

5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE

A) 1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-triflouro-ethanone (3.0 g, 8.70 mmol) was hydrogenated in MeOH (30 ml) under H_2 (45 psi) over $Pd(OH)_2$ (300 mg of 20 wt %/C, 10% wt). After 2.5 hours the reaction was filtered through a Celite pad and rinsed with MeOH (30 ml). The solution was concentrated to a light brown oil which crystallized (2.42 g, 96%). (TLC 10% MeOH/CH_2Cl_2 R_f0.56). APCI MS m/e 286.2[$(M+1)^+$]. mp 129–131° C.

B) 1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,9-pentaene)-2,2,2-trifluoro-ethanone

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone (500 mg, 1.75 mmol) was stirred in THF (2 ml). This mixture was treated with H_2O (2 mL) and glyoxal sodium bisulfite addition compound hydrate (931 mg, 3.50 mmol) then stirred at 55° C. for 2.5 hours. The reaction was cooled to room temperature and extracted with EtOAc (3×40 ml). The combined organic layer was washed with H_2O (2×30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an off white powder (329 mg, 60%). (TLC 25% EtOAc/hexanes R_f0.40). mp 164–166° C.

C) 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene hydrochloride

1-(5,8,14-Triazatetracyclo(10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (320 mg, 1.04 mmol) was slurred in MeOH (2.0 ml) and treated with Na_2CO_3 (221 mg, 2.08 mmol) in H_2O (2.0 ml). The mixture was warmed to 70° C. for 2 hours. then concentrated, treated with H_2O (20 mL) and extracted with CH_2Cl_2 (3×10 ml). The organic layer was dried through a cotton plug and concentrated to give a light yellow oil (183 mg, 83%) which solidified upon standing (mp 138–140° C.). This material

was dissolved in MeOH (10 mL), treated with 3M HCl/EtOAc (3 ml), concentrated and azeotroped with MeOH (2×20 mL) to give solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (208 mg, 97%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.26). ^1H NMR (400 MHz, CD_3OD) δ8.94 (s, 2H), 8.12 (s, 2H), 3.70 (m, 2H), 3.54 (d, J=12.5 Hz, 2H), 3.35 (d, J=12.5 Hz, 2H), 2.49 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). GCMS m/e 211 (M^+). mp 225–230° C.

EXAMPLE 27

14-METHYL-5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]HEXADECA-2(11),3.5.7.9-PENTAENE HYDROCHLORIDE

5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene (207 mg, 0.98 mmol) was treated with 37% aqueous formaline solution (1 mL) and formic acid (1 mL) then warmed to 80° C. for 1 hour. The reaction was poured into water, made basic (NaOH, pH~11) and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and chromatographed on Silica gel to provide a yellow solid. This was stirred in MeOH (2 mL) and treated with 3N HCl EtOAc (2 mL). After concentration the solids were recrystallized from MeOH/Et_2O to afford product as a white solid (70 mg, 27%). (2% MeOH/CH_2Cl_2 (NH_3) R_f 0.47). ^1H NMR (400 MHz, $CDCl_3$) δ8.71 (s, 2H), 7.80 (s, 2H), 3.37 (br s, 2H), 3.03 (m, 2H), 2.47 (m, 2H), 2.32 (m, 1H), 2.18 (br s, 3H), 1.84 (d, J=11.0 Hz, 1H). APCI MS m/e 226.2 [(M+1)$^+$]. mp >250° C.

EXAMPLE 28

5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$] PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (900 mg, 2.61 mmol) and potassium acetate (KOAc) (2.6 g, 26.1 mmol) were dissolved in DMSO (10 mL) and warmed with stirring to 100° C. for 16 hours. The mixture was cooled and diluted with H_2O (50 mL) then extracted with 80% EtOAc/hexanes (6×25 mL). The organic layer was washed with H_2O (3×20 mL), dried (Na_2SO_4), filtered and concentrated and purified by chromatography to give an oil (575 mg, 70%). (TLC 50% EtOAc/hexanes (NH_3) R_f 0.56)

B) 2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (575 mg, 1.82 mmol) was hydrogenated in MeOH under a H_2 atmosphere at (45 psi) over 10% Pd/C (80 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (450 mg, 86%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.6). ^1H NMR (400 MHz, CD_3OD) δ6.67–6.59 (m, 2H), 4.12 (m, 1H), 3.73 (m, 1H), 3.73 (m, 1H), 3.51 (m, 1H), 3.07 (m, 2H), 2.24 (m, 1H), 1.94 (d, J=10.5 Hz, 1H). GCMS m/e 286 (M^+).

C) 2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(1.0),3,6,8-tetraene)-ethanone (Goldstein, S. W.; Dambek, P. J. *J. Het. Chem.* 1990, 27, 335.)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), trimethyl orthoformate (0.19 mL, 1.73 mmol) pyridinium-p-toluenesulfonic acid (PPTS, 18 mg, 0.07 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135° C. for 18 hours. The mixture was cooled, treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered, concentrated and purified by chromatography to give an oil (110 mg, 71%). (TLC 20% EtOAc/hexanes R_f 0.40)

D) 5-Oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$] pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3.6.8-tetraene)-ethanone (110 mg, 0.37 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (78 mg, 0.74 mmol) in H_2O (2 mL). The stirred mixture was warmed to 80° C. for 2 hours. concentrated to solids, diluted with H_2O and extracted with EtOAc (3×40 mL). The product was extracted into aqueous 1N HCl solution (2×40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. The product was extracted with EtOAc (3×40 mL), dried (Na_2SO_4), concentrated and chromatographed on Silica gel to produce an oil. (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.19).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes. After 18 hours, the product was collected by filtration (55 mg, 63%). ^1H NMR (400 MHz, CD_3OD) δ8.47 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 3.41 (m, 2H), 3.30 (m, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.47 (m, 1H), 2.15 (d, J=11.0 Hz, 1H). APCI MS m/e 201.03 [(M+1)$^+$]

EXAMPLE 29

6-METHYL-5-OXA-7,13-DIAZATETRACYCLO [9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo[9.3.1 $0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), triethyl orthoacetate (0.34 mL, 1.83 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135° C. for 18 hours. Workup, isolation and purification as in Example 28C provided the title compound (90 mg, 55%).

B) 6-Methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$] pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (90 mg, 0.30 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (61 mg, 0.58 mmol) in H_2O (3 mL). The stirred mixture was warmed to 80° C. for 2 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3×40 mL). The solution was dried (Na_2SO_4), concentrated, and chromatographed on Silica gel to produce an oil. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.18). ^1H NMR (free base) (400 MHz, $CDCl_3$) δ7.40 (s, 1H), 7.26 (s, 1H), 3.05–2.98 (m, 4H), 2.72 (d, J=12.8 Hz, 2H), 2.59 (s, 3H), 2.46 (m, 1H), 1.98 (d, J=10.5 Hz, 1H).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes. After 18 hours, the product was collected by filtration (10 mg, 13%). APCI MS m/e 215.2 [(M+1)$^+$]. mp >250° C.

EXAMPLE 30

2-FLUORO-N-(5-HYDROXY-10-AZA-TRICYCLO [6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-BENZAMIDE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-ethanone(150 mg, 0.524 mmol), 2-fluorobenzoyl chloride (0.07 mL, 0.576 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol), pyridine (0.046 mL, 0.576 mmol) and xylenes (5 mL) were combined under nitrogen and stirred at 135° C. for 18 hours. After 24 hours, additional PPTS (50 mg) was added and the material stirred at 135° C. for an additional 24 hours. Workup as above provided crude product (145 mg, 0.375 mmol) which was combined with Na_2CO_3(s) (80 mg, 0.75 mmol) in MeOH (5 mL) and H_2O (2 mL) and heated to reflux. After 3 hours, the reaction was cooled and diluted with water then extracted with CH_2Cl_2 (4×40 mL), dried through a cotton plug then chromatographed to remove baseline impurity (5% MeOH/CH_2Cl_2 (NH_3)). The crude material was treated with excess 3N HCl EtOAc and concentrated, then dissolved in a minimum of MeOH and the solution was saturated with Et_2O and stirred. After stirring 4 hours the product was collected by filtration (85 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD) δ7.99 (m, 2H), 7.59 (m, 1H), 7.36–7.23 (m, 2H), 6.82 (s, 1H), 2.99 (m, 4H), 2.78 (m, 2H), 2.35 (m, 1H), 1.96 (d, J=10.5 Hz, 1H). APCI MS m/e 313.1 [(M+1)$^+$]. mp 125–130° C. (subl.).

EXAMPLE 31

4-CHLORO-10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Copper(I)chloride (CuCl) was prepared as follows: $CuSO_4$ (4.3 g) and NaCl (1.2 g) were dissolved in hot H_2O (14 mL). sodium bisulfite ($NaHSO_3$) (1 g) and sodium hydroxide (NaOH) (690 mg) were dissolved in H_2O (7 mL) and added to the hot acidic solution over 5 minutes. The precipitated white solids were filtered and washed with water.

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (460 mg, 1.7 mmol) was dissolved in H_2O (3 mL) and concentrated HCl solution(1 mL) then cooled to 0° C. and treated with a solution of sodium nitrite ($NaNO_2$) (275 mg) in H_2O (1 mL) dropwise. To the resulting solution was added a CuCl (202 mg, prepared as described above, 2.04 mmol) in concentrated HCl solution (2 mL) over 10 minutes (gas evolution observed). The resulting solution was warmed to 60° C. for 15 minutes, then was cooled to room temperature and extracted with EtOAc (4×30 mL). After drying over Na_2SO_4, the solution was filtered and concentrated to an oil which was filtered through a Silica pad to remove baseline material eluting with 50% EtOAc/hexanes to give an oil (470 mg, 95%).

B) 4-Chloro-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (470 mg, 1.62 mmol) and Na_2CO_3 (344 mg, 3.24 mmol) in MeOH (30 mL) and H_2O (10 mL) were heated to reflux. After 2 hours, the reaction was cooled and diluted with water then extracted with EtOAc (4×40 mL), dried (Na_2SO_4), filtered and concentrated to a yellow oil. The crude material was treated with excess 3N HCl EtOAc and concentrated, then dissolved in a minimum of CH_2Cl_2 and the solution was saturated with hexanes and stirred, After stirring 4 hours the product was collected by filtration (155 mg, 42%). ^{1}H NMR (free base) (400 MHz, $CDCl_3$) δ7.15 (m, 2H), 7.09 (d, J=8.0 Hz, 1H), 3.00–2.94 (m, 4H), 2.68, (m, 2H), 2.38 (m, 1H), 1.92 (d, J=10.5 Hz, 1H). ^{1}H NMR (HCl salt) (400 MHz, DMSO-d_6) δ7.30–7.20 (m, 3H), 3.30–3.15 (m, 6H), 2.37 (m, 1H), 1.89 (d, J=11.0 Hz, 1H). APCI MS m/e 194.1 [(M+1)$^+$].

EXAMPLE 32

10-AZATRICYCLO[6.3.1.0–2.7–]DODECA-2(7),3,5-TRIEN-4-YL CYANIDE HYDROCHLORIDE

A) 1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (500 mg, 1.85 mmol) was dissolved in H_2O (5 mL) and concentrated H_2SO_4 solution (0.5 mL) then cooled to 0° C. and treated with a solution of sodium nitrite ($NaNO_2$) (140 mg, 2.04 mmol) in H_2O (3 mL) dropwise. Potassium iodide (460 mg, 2.78 mmol) in 1N H_2SO_4 solution (0.5 mL) was added over 10 minutes (reaction becomes dark red). The resulting solution was warmed to room temperature and stirred 18 hours. The reaction was quenched with $NaHSO_3$ and water (pH 2.5) then extracted with EtOAc (4×30 mL). After drying (Na_2SO_4), the solution was filtered and concentrated to a yellow oil which was chromatographed on Silica gel to provide a yellow oil. (260 mg, 37%). (TLC 30% EtOAc/hexanes R_f 0.70). (A 5.4 g scale performed as above yielded 5 g, 67%).

B) 4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (5 g, 13.1 mmol) and 37% saturated aqueous NH_4OH solution (50 mL)) were stirred in MeOH (250 ml) for 2 hours then concentrated and azeotroped with MeOH (2×50 mL). The resulting product was stirred in 1,4-dioxane (75 mL) and treated with saturated Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (5.71 g, 26.2 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (4×30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel (TLC 20% EtOAc/hexanes) to provide product as an oil (4.9 g, 98%).

C) 4-Cyano-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (Utilizing the methods described in: House, H. O.; Fischer, W. F. *J. Org. Chem.* 1969, 3626.)

CuCN (108 mg, 1.21 mmol) and NaCN (59 mg, 1.21 mmol) were combined in dry DMF (6 mL) and warmed to 150° C. under N_2. Solution occurs in 20 minutes. To this was added 4-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (232 mg, 0.6 mmol) in DMF (3.5 mL) and the mixture was stirred for 18 hours at 150° C., The reaction was cooled and diluted with 50% saturated aqueous NaCl solution and extracted with 50% EtOAc/hexanes (3×30 mL). After drying (Na_2SO_4), filtration and concentration the product was isolated by chromatography (86 mg., 50%). (TLC 20% EtOAc/hexanes R_f 0.28).

D) 10-Azatricyclo[6.3.1.0–2,7–]dodeca-2(7),3,5-trien-4-yl cyanide hydrochloride

4-Cyano-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester was treated with 3N HCl EtOAc (6 mL) and warmed to reflux for 2 hours, then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration (49 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ9.66 (br s, NH), 7.86 (br s, NH), 7.74–7.70 (m, 2H), 7.49 (d, J=7.5 Hz, 1H), 3.33–2.97 (m,

6H), 2.17 (m, 1H), 2.01 (d, J=11.0 Hz, 1H). GCMS m/e 184 (M^+). mp 268–273° C.

EXAMPLE 33

3-(10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIEN-4-YL)-5-METHYL-1,2,4-OXADIAZOLE HYDROCHLORIDE

4-Cyano-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (300 mg, 1 1 mmol) was stirred in EtOH (10 mL). To this hydroxyl amine hydrochloride (382 mg, 5.5 mmol) and NaOH (242 mg, 6.05 mmol) were added and the mixture was warmed to reflux. After 45 minutes, the reaction was cooled, diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow solid (110 mg, 0.35 mmol). This solid was dissolved in pyridine (1 mL) and treated with acetyl chloride (0.03 mL, 0.415 mmol) and warmed to 100° C. for 18 hours. The reaction was cooled, treated with H_2O and extracted with EtOAc. The organic extracts were washed with water and saturated aqueous NaCl solution, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel afforded product (50 mg, 0.15 mmol). (25% EtOAc/hexanes R_f 0.18). This product was treated with 2N HCl MeOH (10 mL), heated to 70° C. for 1 hour, cooled, concentrated and recrystallized from MeOH/Et_2O to provide product (15 mg). APCI MS m/e 242.2 [(M+1)$^+$].

EXAMPLE 34

1-(10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIEN-4-YL)-1-ETHANONE HYDROCHLORIDE

A) 1-(4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(10-Aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2trifluoro-ethanone (253 mg, 1.0 mmol) and AcCl (0.68 mL, 10 mmol) were dissolved in DCE (3 mL) and treated with aluminum chloride ($AlCl_3$) (667 mg, 5.0 mmol). The resulting yellow mixture was stirred for 30 minutes then poured over ice and saturated aqueous $NaHCO_3$ solution. After stirring 20 minutes the mixture was extracted with CH_2Cl_2 (3x30 mL). The organic layer was dried through a cotton plug then concentrated to a orange-yellow oil (255 mg, 86%).

B) 4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.3 g, 4.37 mmol) and 37% aqueous NH_4OH solution (10 mL) were stirred in MeOH (30 ml) for 3 hours, then concentrated and azeotroped with MeOH (2x50 mL). (This product could be converted to an HCl salt directly: see the next example.) The resulting product was stirred in 1,4-dioxane (20 mL) and treated with saturated aqueous Na_2CO_3 solution (5 mL). To this was added di-t-butyldicarbonate (1.91 g, 8.74 mmol). After stirring 2 hours, the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4x30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide an oil (1.3 g, 100%). (TLC 40% EtOAc/hexanes R_f 0.56).

C) 1-(10-Azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-1-ethanone hydrochloride

4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (190 mg, 0.63 mmol) was treated with excess 3N HCl EtOAc and warmed to 70° C. for 1 hour then concentrated and dissolved in a minimum of MeOH. The resulting solution was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (81 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ9.75 (br s, NH), 7.89 (s, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.74 (br s, NH), 7.44 (d, J=8.0 Hz, 1H), 3.33 (br s, 2H), 3.22 (br s, 2H), 3.00 (br m, 2H), 2.5 (s, 3H), 2.17 (m, 1H), 2.02 (d, J=11.0 Hz, 1H). GCMS m/e 201 (M^+). mp 198–202

EXAMPLE 35

10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIEN-4-OL HYDROCHLORIDE

A) Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-4-yl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (2.5 g, 8.41 mmol) and 3-chloroperoxybenzoic acid (m-CPBA) (7.5 g, 42 mmol) were stirred in CH_2Cl_2 (20 mL) and warmed to 40° C. for 18 hours. The mixture was cooled to room temperature, then treated with dimethylsulfide (Me_2S) (3 mL, 40.8 mmol) and stirred 24 hours. The resulting mixture was poured into ice and saturated aqueous Na_2CO_3 solution (100 mL) then extracted with Et_2O (4x40 mL). The organic layer was washed saturated aqueous Na_2CO_3 solution (3x40 mL) then dried (Na_2SO_4), filtered and concentrated to afford an oil (1.83 g, 69%). (TLC EtOAc R_f 0.80).

B) 2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-10-yl)-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-4-yl ester (900 mg, 2.87 mmol) was stirred in MeOH (20 mL) and saturated aqueous $NaHCO_3$ solution (15 mL) for 48 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3x20 mL) then dried through a cotton plug. Chromatography on Silica gel provided pure product (420 mg, 54%). (TLC 5% MeOH/CH_2Cl_2 R_f 0.44). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.05 (m, 1H), 6.70 (m, 1H), 6.62 (m, 1H), 4.32 (m, 1H), 3.84 (m, 1H), 3.48 (m, 1H), 3.21 (br s, 1H), 3.16 (br s, 1H), 3.09 (m, 1H), 2.38 (m, 1H), 1.97 (d, J=11.0 Hz, 1H).

C) 10-Azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-ol hydrochloride

2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-10-yl)-ethanone (50 mg, 0.184 mmol) was dissolved in MeOH/H_2O (3/1, 5 mL), treated with Na_2CO_3(s) (40 mg, 0.369 mmol) and warmed to 65° C. for 2 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3x20 mL) then dried through a cotton plug. Filtration through a Silica gel plug provided an oil (10% MeOH/CH_2Cl_2) which was treated with 3N HCl EtOAc (3 mL) then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (10 mg, 26%). ^{1}H NMR (400 MHz, $CDOD_3$) δ7.16 (d, J=8.0 Hz, 1H), 6.80 (d, J=2.0 Hz, 1H), 6.72 (dd, J=8.0,2.0 Hz, 1H), 3.32–3.28 (4H), 3.09 (dd, J=14.5, 12.0 Hz, 2H), 2.32 (m, 1H) 2.03 (d, J=11.0 Hz, 1H) APCI MS m/e 176.2 [(M+1)$^+$]. mp 308 (dec.) °C.

EXAMPLE 36

7-METHYL-5-OXA-6,13-DIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2,4(8),6,9-TETRAENE HYDROCHLORIDE

A) 1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-4-yl ester (800 mg, 2.55 mmol) was combined with $AlCl_3$ (1.0 g, 7.65 mmol) and warmed to

170° C. for 2 hours. The mixture was cooled and treated with 1N aqueous HCl solution (20 mL), extracted with EtOAc and dried (Na_2SO_4). Chromatography affords an oil (190 mg, 24%). (TLC EtOAc R_f 0.75). ^1H NMR (400 MHz, $CDCl_3$) δ12.58 (s, 0.5H), 12.52 (s, 0.5H), 7.53 (s, 1H), 6.86 (s, 1H), 4.33 (m, 1H), 3.91 (m, 1H), 3.56 (m, 1H), 3.28 (br s, 1H), 3.24 (br s, 1H), 3.14 (m, 1H), 2.35 (m, 1H), 1.97 (br d, J=11.2 Hz, 1H).

B) 2,2,2-Trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone

1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (190 mg, 0.605 mmol), hydroxylamine HCl (99 mg, 1.21 mmol) and NaOAc (118 mg, 1.21 mmol) were combined in MeOH (4 mL) and H_2O (1 mL) and warmed to 65° C. for 18 hours. The mixture was cooled, diluted with H_2O and extracted with EtOAc which was dried (Na_2SO_4), filtered and concentrated to provide a yellow oil (177 mg, 93%).

C) 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0_{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene-ethanone

The above oil, 2,2,2-trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone (177 mg, 0.54 mmol) was stirred in DCE (3 mL), treated with triethylamine (0.4 mL, 2.8 mmol) and acetic anhydride (Ac_2O) (0.3 mL, 2.8 mmol) then stirred 18 hours. The reaction was treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered and concentrated to a yellow oil which was dissolved in anhydrous DMF (3 mL) and treated with 60% NaH in oil (32 mg, 1.08 mmol). After stirring 18 hours, additional 60% NaH in oil was introduced (33 mg) and the mixture was stirred 2 hours. The reaction was quenched with H_2O (5 mL) and extracted with 80% EtOAc/hexanes (3×30 mL). The organic layer was washed with H_2O (3×20 mL), dried (Na_2SO_4), filtered and concentrated and chromatographed to provide an oil (40% EtOAc/hexanes R_f 0.56).

D) 7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene hydrochloride

Utilizing the methods described in Example 9C, 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene-ethanone was converted to the title compound. This was treated with 3N HCl EtOAc (3 mL), concentrated and dissolved in a minimum of CH_2Cl_2 which was saturated with hexanes and stirred. After 18 hours the white crystalline product was collected by filtration (18 mg, 13% overall). ^1H NMR (400 MHz, DMSO-d_6) δ7.72 (s, 1H), 7.63 (s, 1H), 3.42–2.98 (m, 6H), 2.50 (s, 3H), 2.23 (m, 1H), 2.08 (d, J=10.5 Hz, 1H). APCI MS m/e 215.2 [(M+1)$^+$].

EXAMPLE 37

4-(2-Methyl-2H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride and 4-(1-Methyl-1H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1.$0^{2,7}$dodeca-2(7),3,5-triene hydrochloride

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.0 g, 3.3 mmol) and dimethylformamide dimethylacetal (DMF-DMA) (4.0 g, 33.6 mmol) were warmed to 140° C. for 18 hours. After cooling, a crystalline precipitate was filtered and rinsed with EtOAc (690 mg, 58%).

The above solid, 3-dimethylamino-1-(10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-propenone, (200 mg, 0.56 mmol) was dissolved in EtOH (3 mL) and treated with 5N HCl EtOH (0.1 mL) followed by methyl hydrazine (0.6 mmol). The resulting mixture was warmed to 70° C. for 4 hours. The mixture was cooled, diluted with water and extracted with EtOAc, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel provided a 3/1 mixture of regioisomeric products (130 mg, 68%). (TLC 50% EtOAc/hexanes R_f 0.40).

The above oil (130 mg, 0.388 mmol) and Na_2CO_3(s) (82 mg, 0.775 mmol) were stirred in MeOH (10 mL) and H_2O (5 mL) for 18 hours. After cooling the reaction was diluted with water, extracted with CH_2Cl_2 dried through a cotton plug and concentrated. The product was purified by chromatography on Silica gel and concentrated to an oil. The salt was generated with 2N HCl MeOH, concentrated and recrystallized from MeOH/EtOAc to provide a 3/1 mixture of regioisomeric pyrrazoles (85 mg, 58%). (5% MeOH/CH_2Cl_2 (NH_3) R_f 0.25). TFA-precursor APCI MS m/e 336.2 [(M+1)$^+$].

EXAMPLE 38

4,5-DICHLORO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on Campaigne, E.; Thompson, W. *J. Org. Chem.* 1950, 72, 629.)

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (539 mg, 2.1 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with ICl_3 (s) (982 mg, 4.21 mmol). The resulting orange solution was stirred 0.5 hours, poured into saturated aqueous $NaHSO_3$ solution (25 mL), extracted with CH_2Cl_2 (3×25 mL), dried through a cotton plug and concentrated to an oil (570 mg, 84%) (TLC 50% EtOAc/hexanes R_f 0.62).

B) 4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (570 mg, 1.75 mmol) was stirred in MeOH (25 mL) and treated with Na_2CO_3(s) (5 g, 47 mmol) in H_2O (5 mL). The stirred mixture was warmed to 70° C. for 4 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3×40 mL). The product was extracted into 1N aqueous HCl solution (2×40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. Product was extracted with CH_2Cl_2 (3×40 mL), filtered through a cotton plug and concentrated to an oil (400 mg, 100%).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) and concentrated, then dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration (210 mg, 45%). (TLC 50% EtOAc/hexanes (NH_3) R_f 0.08). ^1H NMR (400 MHz, DMSO-d_6) δ7.58 (s, 2H), 3.33–2.97 (m, 6H), 2.18 (m, 1H), 1.99 (d, J=10.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ141.02, 130.60, 126.58, 45.54, 40.55, 38.30. GCMS m/e 227, 229 (M$^+$). mp 283–291° C.

EXAMPLE 39

N^4,N^4-DIMETHYL-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE-4-SULFONAMIDE HYDROCHLORIDE

A) 10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (530 mg, 2.1 mmol) was added

to chlorosulfonic acid (2 mL, 30 mmol) and stirred for 5 minutes. The mixture was quenched with ice, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to provide an oil (640 mg, 87%). (TLC 30% EtOAc/hexanes R_f 0.15).

B) N^4,N^4-Dimethyl-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonamide hydrochloride

10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) was stirred in THF (10 mL) and treated with 40% Me_2NH/H_2O (1.5 mL). After 10 minutes the mixture was concentrated and chromatographed on Silica gel (TLC 30% EtOAc/hexanes R_f 0.31) to provide an oil (256 mg, 78%). This material was dissolved in MeOH (6 mL) and NH_4OH (2 mL) and stirred 18 hours. The mixture was concentrated and azeotroped from MeOH (3×). The resulting oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL), concentrated, dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration as a white powder (163 mg, 59%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.54). ^1H NMR (data, free base) (400 MHz, $CDCl_3$) δ7.64 (m, 2H), 7.41 (d, J=8.0 Hz, 1H), 3.30 (m, 2H), 3.20 (d, J=12.5 Hz, 2H), 3.07 (dd, J=12.5, 2.2 Hz, 2H), 2.69 (s, 6H), 2.45, (m, 1H), 2.00 (d, J=11.0 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ128.43, 124.16, 122.75, 46.67, 46.55, 42.11, 39,44, 37,81. GCMS m/e 266 (M^+). (data HCl salt) ^1H NMR (400 MHz, DMSO-d_6) δ7.68–7.52 (3H), 3.38 (m, 2H), 3.24 (m, 2H), 3.04 (m, 2H), 2.58 (s, 6H), 2.22 (m, 1H), 2.04 (d, J=11.0 Hz, 1H). GCMS m/e 266 (M^+). Anal. Calcd. for $C_{13}H_{18}N_2O_2HCl$: C, 51.56; H, 6.32; N, 9.25. Found C, 51.36; H, 6.09; N, 9.09.

EXAMPLE 40

4-(1-PYRROLIDINYLSULFONYL)-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The pyrrolidine analogue was prepared from 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) as by substituting pyrroline in the coupling step described in Example 39B. The TFA product was isolated as an oil (314 mg, 89%). Deprotection and conversion to the salt as in Example 39B affords a white powder (189 mg, 63%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.60). (TLC 50% EtOAc/hexanes R_f 0.65). ^1H NMR (400 MHz, $CDCl_3$) δ7.66 (d, J=8.0 Hz, 1H), 7.64 (s, 1H), 7.37 (d, J=8.0 Hz, 1H), 3.30–3.15 (m, 8H), 3.00 (m, 2H), 2.39 (m, 1H), 1.98 (d, J=11.5 Hz, 1H), 1.72 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ146.91, 144 08, 136.65, 127.90, 124.18, 122.36, 50.43, 47.87, 46.80, 46.63, 42.11, 39.63, 25.10. APCI MS m/e 293 [(M+1)$^+$]. (data HCl salt) ^1H NMR (400 MHz, DMSO-d_6) δ9.78 (br s, NH), 8.1 (br s, NH), 7.73 (d, J =1.5 Hz, 1H), 7.66 (dd, J=8.0, 1.5 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 3.39–3.01 (10H), 2.21 (m, 1H), 2.04 (d, J=11.0 Hz, 1H), 1.66 (m, 4H). GCMS m/e 292 (M^+). Anal. Calcd. For $C_{13}H_{18}N_2O_2HCl.1/2MeOH$: C, 54.07; H, 6.47; N, 8.51. Found C, 53.98; H, 6.72; N, 8.12.

EXAMPLE 41

5,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2,4(8),9-TRIEN-6-ONE HYDROCHLORIDE

(The title compound was prepared following the procedures described in Quallich, G. J.; Morrissey, P. M. *Synthesis* 1993, 51–53, treating 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester as an equivalent to an ortho fluoro phenyl moiety.) ^1H NMR (400 MHz, DMSO-d_6) δ10.42 (s, NH), 9.88 (br s, NH), 7.52 (br s, 1H), 7.15 (s, 1H), 6.79 (s, 1H), 3.41 (d, J=5.0 Hz, 2H), 3.35–3.13 (m, 4H), 2.93 (m, 2H), 2.12 (m, 1H), 1.95 (d, J=11.5 Hz, 1H). APCI MS m/e 215.2 [(M+1)$^+$].

EXAMPLE 42

6-OXO-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

(For references, see: Nachman, R. J. *J. Het. Chem.* 1982, 1545.)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (317 mg, 1.11 mmol) was stirred in THF (10 mL), treated with carbonyldiimidazole (269 mg, 1.66 mmol) and warmed to 60° C. for 18 hours. The mixture was concentrated, diluted with CH_2Cl_2 (50 mL) and washed with 1N aqueous HCl solution (3×10 mL). The organic layer was dried through a cotton plug, concentrated and chromatographed on Silica gel (50% EtOAc/Hexanes) to provide an oil (130 mg). This material converted to the title compound by the methods described in Example 9C. ^1H NMR (400 MHz, DMSO-d_6) δ11.78 (s, NH), 9.56 (br s, NH), 7.63 (br s, NH), 7.24 (s, 1H), 7.07 (s, 1H), 3.26 (br s, 2H), 3.16 (br t, J=9.5 Hz, 1H), 2.93 (br s, 1H), 2.18 (m, 1H), 1.97 (d, J=11.0 Hz,1H). APCI MS m/e 217.2 [(M+1)$^+$].

EXAMPLE 43

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

(See Grunewald, G. L.; Paradkar, V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall, D. J.; Seibel, W. L.; Reitz, T. J. *J. Org. Chem.* 1983, 48, 2321–2327 Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* 1987, 30, 2191–2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^1H NMR (400 MHz, CD_3OD) δ7.67–7.50 (3H), 3.65 (br s, 1H), 3.49–3.42 (m, 2H), 3.29 (s, 1H), 3.28–3.16 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=11.5 Hz, 1H). APCI MS m/e 228.2 [(M+1)$^+$]. (HCl salt) mp 275–277° C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.83; N, 5.16.

EXAMPLE 44

3-PHENYL-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene and 5-iodo-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* 1976, 98, 753–761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* 1977, 99, 3723–3733.)

Magnesium turnings (9.37 g, 385 mmol) were stirred in anhydrous THF (1000 mL) in a flame dried 2L 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter. magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,6-Difluoro-iodobenzene (0.3 g) was added followed by of 3N EtMgBr in THF (0.3 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (24.24 g, 367 mmol) and 2,6-difluoro-iodobenzene (88.0 g, 367 mmol). Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4×). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of

the contents of the addition funnel. The reaction was then maintained at reflux for ~1 hour (no SM by GCMS).

The reaction was cooled to room temperature and quenched with H_2O (200 mL) followed by aqueous 1N HCl solution (200 mL) to dissolve the solids. Product was extracted with hexanes (4×150 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (150 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil (70 g). Chromatography on Silica gel eluting with hexanes provided two lots (9.0 and 21.0 g), which contained primarily 5-iodo-1,4-dihydro-1,4-methano-naphthalene. (TLC hexanes R_f 0.63).

B) 5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

5-Iodo-1,4-dihydro-1,4-methano-naphthalene (20 g) and N-methyl morpholine N-oxide (17.61 g, 130 mmol) were stirred in acetone (90 mL) and H_2O (13 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5% wt, solution in t-BuOH, 0.02 mmol). After 144 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for ½ hour. The mixture was filtered through a Celite pad and the filtrate concentrated to produce an oil which was purified by chromatography on Silica gel eluting with a gradient of hexanes to 100% EtOAc to provide a yellow solid (13.73 g). APCI MS m/e 301.1 [(M−1)$^+$].

C) 10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (8.33 g, 27.6 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichlorocthanc (25 mL) and H_2O (75 mL) then treated with sodium periodate (6.17 g, 29.0 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2×40 mL). The combined organic layer was washed with H_2O (4×30 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (30 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (3.16 mL, 29.0 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0° C.) mixture of $NaHB(OAc)_3$ (18.72 g, 88.0 mmol) in DCE (150 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (6.3 g, 61%). (TLC 5% EtOAc/hexanes R_f 0.10). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.61 (d, J=8.0 Hz, 1H), 7.28–7.22 (m, 3H), 7.13 (d, J=8.0 Hz, 1H), 6.98–6.94 (m, 3H), 3.58 (AB dd, J=14.2 Hz, 2H), 3.26 (br s, 1H), 3.21 (br s, 1H), 3.04 (br d, J=10.2 Hz, 1H), 2.83 (br d, J=10.2 Hz, 1H), 2.47 (d, J=10.0 Hz, 1H), 2.39 (d, J=10.0 Hz, 1H), 2.34 (m, 1H), 1.72 (d, J=10.5 Hz, 1H). APCI MS m/e 376.0 [(M+1)$^+$].

D) 10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

(For a discussion, see: Miyaura, N.; Suzuki, A *Chem. Rev.* 1995, 95. 2457–2483.)

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (375.3 mg, 1.0 mmol), potassium acetate (785 mg, 8.0 mmol) and phenyl boronic acid (183 mg, 1.5 mmol) were combined in 10/1 EtOH/H_2O (5 mL). The mixture was degassed (3 vacuum/N_2 cycles), treated with tetrakis (triphenylphosphine)palladium(0) (57.5 mg, 0.05 mmol) and warmed to 90° C. for 18 h. The reaction was cooled, diluted with H_2O and extracted with Et_2O (3×50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to provide an oil (180 mg, 55%). (TLC 4% EtOAc/hexanes R_f 0.18). GCMS m/e 325 (M)$^+$.

E) 3-Phenyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene was converted into the title compound utilizing the conditions described in Example 2D. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.30). (data for free base) ^{1}H NMR (400 MHz, $CDCl_3$) δ7.46–7.15 (8H), 3.17 (br s, 1H), 3.01 (m, 2H), 2.93 (d, J=13.0 Hz, 1H), 2.72 (dd, J=10.5,2.5 Hz, 1H), 2.63 (dd, J=10.5,2.5 Hz, 1H), 2.41 (m, 1H), 1.91 (d, J=10.5 Hz, 1H). APCI MS m/e 236.2 [(M+1)$^+$]. (HCl salt) mp 262–265° C. Anal. Calcd, for $C_{17}H_{17}N.HCl.1/3H_2O$: C, 73.26; H, 6.86 N, 5.19. Found C, 73.50; H, 6.77; N, 5.04.

EXAMPLE 45

3-HYDROXY-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3.5-triene (3.0 g, 7.99 mmol) was stirred in anhydrous THF (40 mL) at −78° C. under nitrogen and treated dropwise with n-BuLi (3.84 mL of 2.5 M soln, in hexanes, 9.59 mmol). After 10 minutes, tri-isopropylborate (4.61 mL, 20.0 mmol) was added dropwise. After ~½ hour, the reaction was poured into saturated aqueous $NaHCO_3$ solution, stirred 5 minutes and extracted with EtOAc (3×50 mL) and concentrated. The residue was dissolved in 30% Et_2O/hexanes and extracted with 1N NaOH aqueous solution (4×50 mL). The combined aqueous basic layer was treated with concentrated HCl to achieve pH 8 and extracted with EtOAc (4×25 mL), dried (Na_2SO_4) and stripped. Chromatography on Silica gel eluting first with 3% EtOAc/hexanes to remove non-polar components, then with 5% MeOH/CH_2Cl_2 provides the title compound, (TLC 25% EtOAc/hexanes R_f 0.60).

B) 10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (140 mg, 0.48 mmol) dissolved in THF (5 mL) was treated with N-methylmorpholine-N-oxide (64.5 mg, 0.48 mmol) and brought to reflux for 1 hour. The reaction was concentrated and chromatographed on Silica gel to provide product. (TLC 25% EtOAc/hexanes R_f 0.18). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.18–7.15 (3H), 7.04 (dd, J=8.0,7.0 Hz, 1H), 6.95 (m, 2H), 6.75 (d, J=7.0 Hz, 1H), 6.59 (dd, J=8.0,1.0 Hz, 1H), 3.53 (br s, OH), 3.51 (AB d, J=14.0 Hz, 2H), 3.28 (br s, 1H), 3.06 (br s, 1H), 2.91 (dd, J=8.5, 1.5 Hz, 1H), 2.79 (ddd, J=8.5,1.5,1.5 Hz, 1H), 2.42 (d, J=11.0 Hz, 1H), 2.39 (d, J=11.0 Hz, 1H), 2.23 (m, 1H), 1.65 (d, J=10.5 Hz, 1H). APCI MS m/e 266.5 [(M+1)$^+$].

C) 3-Hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (160 mg, 0.60 mmol) was converted into the title compound by the methods described in Example 1D. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.15 (dd, J=8.0,7.5 Hz, 1H), 6.84 (d, J=7.5 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 3.51 (br s, 1H), 3.33–3.25 (3H), 3.16 (d, J=12.0 Hz, 1H), 3.09 (d, J=12.0 Hz, 1H), 2.29 (m, 1H), 2.02 (d, J=11.0 Hz, 1H). APCI MS m/e 175.8 [(M+1)$^+$]. (HCl salt) mp 253–255° C.

EXAMPLE 46

4,5-DIFLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$] DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2,4,5-trifluorobromobenzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.31 (t, J=8.5 Hz, 2H), 3.48–3.13 (6H), 2.38 (m, 1H), 2.11 (d, J=11.5 Hz, 1H). APCI MS m/e 196.2 [(M+1)$^+$]. (HCl salt) mp 301–303° C. Anal. Calcd. for $C_{11}H_{11}F_2N.HCl.1/6H_2O$: C, 56.30; H, 5.30; N, 5.97. Found C, 56.66; H, 5.41; N, 5.96.

EXAMPLE 47

6-ETHYL-5-OXA-7,13-DIAZATETRACYCLO [9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10yl)-ethanone and propionyl chloride were converted to the title compound following the procedures described in Example 30 and Goldstein, S. W.; Dambek. P. J, *J. Het. Chem.* 1990, 27, 335. ^{1}H NMR (400 MHz, CD_3OD) δ7.64 (s, 1H), 7.62 (s, 1H), 3.48 (d, J=2.5 Hz, 2H), 3.41 (d, J=12.0 Hz, 2H), 3.20 (2H), 3.01 (q, J=7.5 Hz, 2H), 2.45 (m, 1H), 2.17 (d, J=11.5 Hz, 1H), 1.42 (t, J=7.5 Hz, 3H). APCI MS m/e 229.2 [(M+1)$^+$].

EXAMPLE 48

6-ISOPROPYL-5-OXA-7,13-DIAZATETRACYCLO [9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and isobutyryl chloride were converted to the title compound following the procedures described in EXAMPLE 47. (TLC 25% EtOAc/hexanes R_f 0.14). ^{1}H NMR (400 MHz, CD_3OD) δ7.65 (2H), 3.49 (br s, 2H), 3.41 (d, J=12.0 Hz, 2H), 3.33–3.19 (3H), 2.45 (m, 1H), 2.18 (d, J=11.5 Hz, 1H), 1.45 (d, J=7.0 Hz, 6H). APCI MS m/e 243.2 [(M+1)$^+$]. (HCl salt) mp 249–251° C.

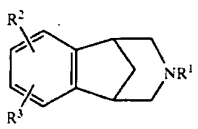
EXAMPLE 49

6-BENZYL-5-OXA-7,13-DIAZATETRACYCLO [9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and phenyl-acetyl chloride were converted to the title compound following the procedures described in EXAMPLE 47. ^{1}H NMR (400 MHz, CD_3OD) δ7.63 (s, 1H), 7.58 (s, 1H), 7.36–7.24 (5H), 4.29 (s, 2H), 3.46 (d, J=2.5 Hz, 2H), 3.39 (d, J=12.0 Hz, 2H), 3.18 (2H), 2.42 (m, 1H), 2.15 (d, J=11.5 Hz, 1H). APCI MS m/e 291.2 [(M+1)$^+$].

What is claimed is:

1. A compound of the formula



(I)

R^1 is hydrogen, $(C_1–C_6)$alkyl, unconjugate $(C_3–C_6)$ alkenyl, $XC(=O)R^{13}$, benzyl or $—CH_2CH_2—O—(C_1–C_4)$alkyl;

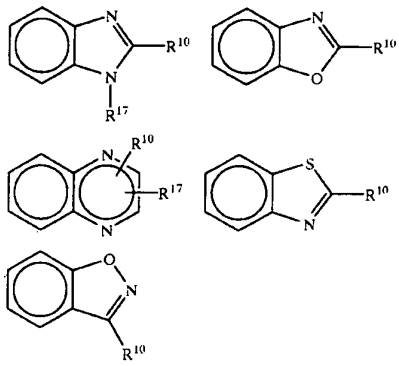
R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo rings shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents that are selected, independently, from $(C_1–C_6)$ alkyl optionally substituted with from one to seven fluorine atoms; $(C_1–C_6)$alkoxy optionally substituted with from one to seven fluorine atoms; nitro, cyano, halo, $(C_2–C_6)$ alkenyl, $(C_2–C_6)$alkynyl, hydroxy, amino, $(C_1–C_6)$ alkylamino and $((C_1–C_6)alkyl)_2$amino, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ and $—XC(=O)R^{13}$;

wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and $(C_1–C_6)$ alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, $—N—(C_1–C_6)$ alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, $(C_1–C_6)$alkylene;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^2 and R^3, together with the benzo of formula I, form a bicyclic ring system selected from the following:



wherein R^{10} and R^{17} are selected, independently, from $(C_1–C_6)$ alkyl optionally substituted with from one to seven fluorine atoms; $(C_1–C_6)$ alkoxy optionally substituted with from one to seven fluorine atoms; $(C_2–C_6)$alkenyl, $(C_2–C_6)$ alkynyl, hydroxy, amino, $(C_1–C_6)$alkylamino and $((C_1–C_6)$ alkyl)$_2$amino, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ and $—XC(=O)R^{13}$ and wherein R^4, R^5, R^6, R^7, R^8 and R^{13} are as defined in claim 1.

3. A compound according to claim 1 selected from the group consisting of:

5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

and pharmaceutically acceptable salts thereof.

4. A compound according to claim **1** which is:

6-methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim **1** which is:

6-methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

or a pharmaceutically acceptable salt thereof.

6. A compound according to claim **1** which is:

6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

or a pharmaceutically acceptable salt thereof.

7. A compound according to claim **1** which is:

6,7dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

or a pharmaceutically acceptable salt thereof.

8. A compound according to claim **1** which is:

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

or a pharmaceutically acceptable salt thereof.

9. A compound according to claim **1** which is:

14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim **1** which is:

5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

or a pharmaceutically acceptable salt thereof.

11. A compound according to claim **1** which is:

7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;

or a pharmaceutically acceptable salt thereof.

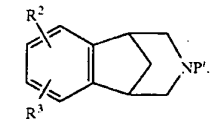
12. A pharmaceutical composition comprising an amount of a compound according to claim **1** and a pharmaceutically acceptable carrier.

13. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim **1** that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

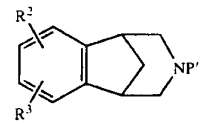
14. A method for treating a disorder or condition selected from inflammatory bowel disease, ulcerative colitis, pyoderma gangrenosum, Crohn's disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions; dependencies on, or addictions to, nicotine, tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound according to claim **1** that is effective in treating such disorder or condition.

15. A compound of the formula (I')

(I')



(I')



wherein

R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents that are selected, independently, from (C_1–C_6) alkyl optionally substituted with from one to seven fluorine atoms; (C_1–C_6)alkoxy optionally substituted with from one to seven fluorine atoms; nitro, cyano, halo, (C_2–C_6) alkenyl, (C_2–C_6)alkynyl, hydroxy, amino, (C_1–C_6) alkylamino and ((C_1–C_6)alkyl)$_2$amino, —CO_2R^4, —$CONR^5R^6$, —$SO_2NR^7R^8$, —C(=O)R^{13} and —XC(=O)R^{13};

wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1–C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, —N—(C_1–C_6) alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1–C_6)alkylene;

and P' is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or (C_1-C_6)alkyl; $—C(=O)NR^5R^6$ wherein R^5 and R^6 are selected, independently, from hydrogen and (C_1-C_6) alkyl, or R^5 and R^6 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, —N—(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; —C(=O)H, $—C(=O)(C_1-C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms; benzyl, or t-butoxycarbonyl (t-Boc).

* * * * *

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BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
14-Sep-99	Submission to FDA	Initial IND
20-Sep-99	Correspondence from FDA	Initial IND acknowledgement
22-Sep-99	Response to FDA	Response to 20-Sep-99 request for IND desk copies
13-Oct-99	Submission to FDA	Clinical
22-Oct-99	Submission to FDA	Change in Protocol
26-Jan-00	Submission to FDA	New Protocol; CMC
23-Feb-00	Submission to FDA	New Investigator; Revised FDA-1572 Form
9-Mar-00	Response to FDA	Response to FDA 1&2-May request for pk protocol and safety tables
31-Mar-00	Response to FDA	Response to FDA Request for Information; clinical agreements 21-Mar-00
5-Apr-00	Correspondence from FDA	Minutes of Phase 2 Study Protocol 1002 telecon
19-Apr-00	Response to FDA	Response to FDA 21-Mar-00 Request, Amendment to Study Protocol 1002
22-May-00	Submission to FDA	New Investigator
22-May-00	Correspondence from FDA	Comments on Phase 2 Study Protocol 1002 amendment
25-May-00	Submission to FDA	Clinical
8-Jun-00	Submission to FDA	CMC
27-Jun-00	Submission to FDA	Safety Report
29-Jun-00	Submission to FDA	New Investigator
14-Jul-00	Submission to FDA	New Protocol; New Investigator
21-Jul-00	Submission to FDA	New Investigators; CMC
18-Aug-00	Submission to FDA	New Investigator
6-Sep-00	Submission to FDA	Investigator's Brochure
29-Sep-00	Submission to FDA	Protocol Amendment; New Investigator; Toxicology
6-Oct-00	Submission to FDA	IND Annual Report
26-Oct-00	Submission to FDA	New Protocol; New Investigator; CMC
1-Nov-00	Submission to FDA	New Protocol; New Investigator; CMC
6-Dec-00	Correspondence from FDA	Recommendation for smoking status in Study 1006
12-Dec-00	Submission to FDA	Revised FDA 1572 Forms;Toxicology
9-Jan-01	Submission to FDA	Amendment to Study Protocol 1006
7-Mar-01	Submission to FDA	Revised FDA 1572 Forms;CMC
13-Mar-01	Response to FDA	Response to FDA re Study 1006 smoking status telecons 7Dec2000&22Feb2001
22-Mar-01	Submission to FDA	Revised FDA 1572 Form
6-Apr-01	Correspondence from FDA	Preclinical questions on initial IND
9-Apr-01	Submission to FDA	Toxicology
30-May-01	Submission to FDA	New Protocol, New Investigator, Chemistry, Manufacturing & Controls
7-Jun-01	Submission to FDA	Change in Protocol; Revised FDA-1572 Form
8-Jun-01	Response to FDA	FDA on review of IND and Phase 2 Program. Responses 31-Mar-00, 1-Apr-00, 25-May-00
28-Jun-01	Submission to FDA	General Correspondence: Request for Meeting to discuss Study 1002 results
16-Jul-01	Submission to FDA	New Protocol;New Investigator;Clinician's CV;Revised FDA-1572 Forms
23-Jul-01	Correspondence from FDA	Date for Type C meeting Sept 5 2001
17-Aug-01	Submission to FDA	General Correspondence: Briefing Package for Sept 5 2001 meeting
24-Aug-01	Submission to FDA	New Investigators; Toxicology
18-Sep-01	Submission to FDA	New Protocol; New Investigator; CMC

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
26-Sep-01	Correspondence from FDA	Minutes of Type C meeting Sept 5 2002
27-Sep-01	Submission to FDA	New Protocol; New Investigator; CMC
18-Oct-01	Submission to FDA	IND Annual Report
18-Oct-01	Submission to FDA	New Investigator; CMC
29-Oct-01	Submission to FDA	New Protocol; New Investigator
5-Nov-01	Submission to FDA	New Protocol; New Investigator
16-Nov-01	Submission to FDA	Meeting Minutes from 5Sept2001; New Protocol; Revised FDA-1572 Forms; CMC
20-Nov-01	Submission to FDA	New Investigators; Revised FDA 1572 Form
14-Dec-01	Submission to FDA	New Investigator; Investigator Brochure
20-Dec-01	Submission to FDA	New Protcol; New Investigator
21-Dec-01	Submission to FDA	Information amendment, Clinical
10-Jan-02	Submission to FDA	Change in Protocols; New Investigators
11-Feb-02	Submission to FDA	New Investigators
8-Mar-02	Submission to FDA	Protocol, CMC
14-Mar-02	Submission to FDA	New Protocol, Protocol Change
19-Mar-02	Submission to FDA	Change in Protocols; New Investigators
2-Apr-02	Submission to FDA	Change in Protocols; New Investigators
8-Apr-02	Submission to FDA	New Protocol; New Investigators
25-Apr-02	Submission to FDA	New Investigator;Revised FDA-1572 Forms;CMC
25-Apr-02	Submission to FDA	Protocol Change
29-Apr-02	Submission to FDA	Toxicology
2-May-02	Submission to FDA	Request for Special Protocol Assesment
7-May-02	Submission to FDA	Request for Special Protocol Assessment
22-May-02	Submission to FDA	New Investigators; Revised FDA-1572 Forms;Toxicology
5-Jun-02	Response to FDA	Response to FDA request for information 3-Jun-02, Toxicology
13-Jun-02	Correspondence from FDA	Further CAC recommendations
26-Jun-02	Submission to FDA	New Investigators, Revised FDA 1572 Forms
3-Jul-02	Submission to FDA	Request for Special Protocol Assessment, Info Amendment - Pharm/Tox
11-Jul-02	Response to FDA	9-Jul-02 FDA request for information, Pharmacology
16-Jul-02	Submission to FDA	Revised FDA 1572 Forms; Update IB
2-Aug-02	Correspondence from FDA	CAC recommendations
16-Aug-02	Submission to FDA	New Investigator, Revised FDA 1572 Forms
28-Aug-02	Submission to FDA	Protocol, New Investigator, CMC, Labels, Investogator CV
6-Sep-02	Submission to FDA	New Investigator, CMC
12-Sep-02	Submission to FDA	General Correspondence: EOP2 Meeting Request
1-Oct-02	Submission to FDA	CMC, Toxicology
4-Oct-02	Submission to FDA	New Investigator, Revised FDA 1572 Forms
21-Oct-02	Correspondence from FDA	Date for End of Phase 2 meeting
29-Oct-02	Submission to FDA	IND Annual Report
7-Nov-02	Submission to FDA	End of Phase 2 Meeting Package
8-Nov-02	Submission to FDA	Investigator's Brochure
15-Nov-02	Submission to FDA	New Protocol; Revised FDA 1572 Form; CMC
27-Nov-02	Response to FDA	Response to FDA Questions 26-Nov-02 Quit rates

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
17-Dec-02	Submission to FDA	Minutes: End-of-Phase 2 Meeting
17-Dec-02	Submission to FDA	New Investigators; CMC
3-Jan-03	Submission to FDA	General Correspondence: Response to FDA's 31Dec2002 recommendation for Study 1024
6-Feb-03	Correspondence from FDA	Minutes of End of Phase 2 meeting
6-Feb-03	Submission to FDA	Revised FDA 1572 Forms, General Correspondence: USAN Name
7-Feb-03	Submission to FDA	New Protocol Study 1035
7-Mar-03	Submission to FDA	New Investigator, January 2003 Erratum, New contact
19-Mar-03	Submission to FDA	Change in Protocol Study 1024; New Investigator
10-Apr-03	Submission to FDA	Revised FDA 1572 Form; CMC
9-May-03	Submission to FDA	Change in Protocol Study 1035; New Investigator; Revised FDA 1572 Form
3-Jun-03	Submission to FDA	Change in Protocols Studies 1018 and 1019; New Investigator; Revised FDA 1572 Form
9-Jun-03	Submission to FDA	New Protocol Study 1028, New Investigator, CMC
26-Jun-03	Submission to FDA	New Protocol Study 1036; New Investigator; Revised FDA 1572 Forms
1-Jul-03	Submission to FDA	Revised FDA 1572 Form
11-Jul-03	Submission to FDA	New Investigators
16-Jul-03	Submission to FDA	New Protocol Study 1031; New Investigator
13-Aug-03	Submission to FDA	New Investigators; Revised FDA 1572 Forms
15-Aug-03	Submission to FDA	General Correspondence Request for Meeting CMC/EOP2
21-Aug-03	Correspondence from FDA	Comments on inclusion criteria in 1028 and 1036
27-Aug-03	Submission to FDA	New Investigators, Revised FDA 1572 Forms; CMC
27-Aug-03	Submission to FDA	General Correspondence: Request for Meeting (CMC)
28-Aug-03	Response to FDA	General Correspondence - Response to Request for Information
4-Sep-03	Correspondence from FDA	Date and details for EOP2 (CMC) meeting
10-Sep-03	Submission to FDA	End of Phase 2 CMC Meeting Information: Pre-meeting Information Package for CMC
18-Sep-03	Submission to FDA	Protocol Amendments for studies 1028 & 1036, New Investigators, Revised FDA 1572
25-Sep-03	Submission to FDA	New Protocols, New Investigators
10-Oct-03	Submission to FDA	New Protocols, New Investigators, CMC
20-Oct-03	Submission to FDA	New Protocol; New Investigator
5-Nov-03	Submission to FDA	New Investigators; Revised FDA 1572 Forms; CMC
7-Nov-03	Submission to FDA	New Protocol; New Investigator
11-Nov-03	Correspondence from FDA	FDA EOP2 (CMC) minutes
13-Nov-03	Submission to FDA	IND Annual Report
2-Dec-03	Submission to FDA	New Investigators, Revised FDA 1572 Forms
9-Dec-03	Submission to FDA	Investigator's Brochure
22-Dec-03	Submission to FDA	General Correspondence: EOP2 meeeting minutes clarification; abuse liability briefing
15-Jan-04	Submission to FDA	New Investigators, Revised FDA 1572 Forms
13-Feb-04	Submission to FDA	Safety Letter
10-Mar-04	Submission to FDA	New Investigators, Revised FDA 1572 Forms, IB Addendum
22-Mar-04	Correspondence from FDA	Request for additional information re abuse potential briefing document
23-Mar-04	Submission to FDA	Information Amendment CMC
30-Mar-04	Submission to FDA	Pharmacology/Toxicology
7-Apr-04	Submission to FDA	Safety Report
13-Apr-04	Submission to FDA	Response to abuse potential questions, New Investigator, Revised FDA 1572 Forms

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
3-May-04	Submission to FDA	CMC; Revised FDA 1572 Forms
12-May-04	Submission to FDA	Safety Report
21-May-04	Submission to FDA	General Correspondence - Clinical; request for feedback on P3 narratives proposal
26-May-04	Submission to FDA	CMC
1-Jun-04	Submission to FDA	Safety Letter
22-Jun-04	Submission to FDA	Revised FDA 1572 Forms
14-Jul-04	Submission to FDA	Meeting Request to discuss CMC related NDA filing strategies
6-Aug-04	Submission to FDA	Revised FDA 1572 Forms
23-Aug-04	Submission to FDA	Safety Letter
31-Aug-04	Submission to FDA	Safety Letter
13-Sep-04	Submission to FDA	Pre meeting Information Package for CMC
21-Sep-04	Submission to FDA	New Protocol, New Investigator
28-Sep-04	Submission to FDA	New Protocols, New Investigators, CMC
19-Oct-04	Submission to FDA	IND Annual Report
20-Oct-04	Submission to FDA	General Correspondence: Tradename proposal
2-Nov-04	Submission to FDA	Toxicology, Clinical Study Report, Revised FDA 1572 Forms
5-Nov-04	Submission to FDA	Follow up Safety Letter
10-Nov-04	Response to FDA	General Correspondence: Summary of Agreements from Type C CMC Meeting
9-Dec-04	Submission to FDA	New Protocol, New Investigator, CMC, Revised FDA 1572 Forms
21-Dec-04	Correspondence from FDA	Meeting Minutes 14Oct04
22-Dec-04	Response to FDA	responses to issues raised in 13Apr04 assessment of amendment dated 13apr04 re
6-Jan-05	Submission to FDA	New Investigator, New Protocol
21-Jan-05	Response to FDA	Comments on FDA meeting minutes re comparability protocols from 14Oct04 CMC
4-Feb-05	Submission to FDA	Toxicology reports, Protocol Amendment, New Protocol, New Investigator, Revised FDA
11-Feb-05	Submission to FDA	Clinical, CMC
25-Feb-05	Submission to FDA	Request for a pre-NDA meeting
11-Mar-05	Submission to FDA	New Investigator, CMC
23-Mar-05	Correspondence from FDA	Letter confirming date of Pre-NDA meeting
1-Apr-05	Submission to FDA	Safety Letter
5-Apr-05	Submission to FDA	Protocol Amendment - New Investigators; Revised FDA 1572 Form
18-Apr-05	Submission to FDA	Comparability Protocol
22-Apr-05	Submission to FDA	Information amendment: Statistical analysis plan
22-Apr-05	Submission to FDA	Information Amendment Clinical
5-May-05	Submission to FDA	New Investigators, Revised FDA 1572 Forms
6-May-05	Submission to FDA	General Correspondence statistical analysis plan for Study 1039
10-May-05	Submission to FDA	Briefing Document for Pre-NDA meeting
11-May-05	Response to FDA	Response to FDA questions related to Statistical Analysis Plan
17-May-05	Submission to FDA	New Protocol, New Investigator, CMC, Revised FDA 1572 Forms
27-May-05	Submission to FDA	Safety Letter
20-Jun-05	Response to FDA	Response to FDA Request for Information from the Pre-NDA meeting
22-Jun-05	Submission to FDA	New Investigator, CMC, Revised FDA 1572 Forms
30-Jun-05	Submission to FDA	Comparability Protocol
3-Aug-05	Submission to FDA	Proposed Comprehensive Quality Overview Summary for the Varenicline Tartrate NDA

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
3-Aug-05	Submission to FDA	Protocol Change
23-Sep-05	Submission to FDA	General Correspondence -PRO document
4-Oct-05	Submission to FDA	General Correspondence: Request for meeting with Office of New Drug Chemistry
11-Oct-05	Submission to FDA	New Protocol, CMC, Revised FDA 1572 Forms
24-Oct-05	Submission to FDA	General Correspondence: Feedback on FDA minutes from 18 Aug 2005 Abuse Liability
9-Nov-05	Submission to FDA	New Drug Application
21-Nov-05	Submission to FDA	General Correspondence: NDA Safety Update Proposal
2-Dec-05	Submission to FDA	Annual Report
8-Dec-05	Submission to FDA	New Protocols; CMC
6-Jan-06	Correspondence from FDA	Meeting minutes from 9Jun05 Pre-NDA meeting
13-Jan-06	Submission to FDA	Type C Meeting Request
27-Jan-06	Submission to FDA	New Investigators, Revised FDA 1572 Forms, Clinical
3-Feb-06	Response to FDA	FDA Query received 25Jan06 related to report links and study locations
7-Feb-06	Submission to FDA	Stability Update
9-Feb-06	Submission to FDA	3 mo Safety Udate
13-Feb-06	Response to FDA	FDA Query received 27Jan06 related to Qualifying Procedures and report datasets
3-Mar-06	Response to FDA	FDA request received 28Feb06 for reconciliation and data
3-Mar-06	Submission to FDA	Request for pre-approval importation
10-Mar-06	Submission to FDA	New protocol, New Investigators and Revised FDA 1572 Forms
8-Mar-06	Response to FDA	FDA request received 6Mar06 for updated CTD sections
10-Mar-06	Response to FDA	FDA request received 3Mar09 for histories and measures tables
14-Mar-06	Response to FDA	FDA letter received 6Mar06 regarding Trade Name
14-Mar-06	Response to FDA	FDA request received 3Mar06 dependence
14-Mar-06	Response to FDA	FDA request received 7Mar06 for AE tables
15-Mar-06	Response to FDA	FDA request received 10Mar06 for QT data
23-Mar-06	Response to FDA	FDA request received 20Mar06 SAEs
24-Mar-06	Response to FDA	FDA request received 21Mar06 for different presentation of table
27-Mar-06	Response to FDA	FDA request received 23Mar06 for data
29-Mar-06	Response to FDA	FDA Query received 20Mar06 related to interpretation of CPK values
31-Mar-06	Response to FDA	FDA request received 27Mar06 for new AE data
31-Mar-06	Response to FDA	FDA request received 30Mar06 for data
7-Apr-06	Response to FDA	FDA request received 31Mar06 for data tables
11-Apr-06	Response to FDA	Quality Queries
20-Apr-06	Response to FDA	Quality Queries Received 24Feb and 13Mar06
1-May-06	Response to FDA	Follow to 27Apr06 telecon related to dosing
4-May-06	Response to FDA	Quality Queries 21April and May4,06
9-May-06	Response to FDA	Quality Queries 05May06
10-May-06	Correspondence from FDA	FDA letter received May 5 and telecon May 9 regarding package label
11-May-06	Submission to FDA	Final Printed Label and Promotional Materials

#13

UNITED STATES PATENT AND TRADEMARK OFFICE

OCT 30 2006

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Office of Regulatory Policy
HFD-7
5600 Fishers Lane (Rockwall II Rm 1101)
Rockville, MD 20857

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 6,410,550 was filed on June 28, 2006, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, Chantix™ (varenicline), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: A. David Joran
Pfizer Inc.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 26 2007

Re: Chantix
Docket No. 2007E-0010

The Honorable Jon Dudas
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Box Patent Extension
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Dudas:

This is in regard to the application for patent term extension for U.S. Patent No. 6,410,550 filed by Pfizer, Inc. under 35 U.S.C. § 156. The human drug product claimed by the patent is Chantix (varenicline), which was assigned NDA No. 21-928.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in *Glaxo Operations UK Ltd. v. Quigg*, 706 F. Supp. 1224 (E.D. Va. 1989), *aff'd*, 894 F. 2d 392 (Fed. Cir. 1990).

The NDA was approved on May 10, 2006, which makes the submission of the patent term extension application on June 28, 2006, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: A. David Joran
Pfizer Inc.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Office of Regulatory Policy
HFD - 7
5600 Fishers Lane (Rockwall II Rm. 1101)
Rockville, MD 20857

MAR - 1 2007

Attention: Beverly Friedman

Dear Ms. Axelrad:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 6,410,550. The application was filed on June 28, 2006, under 35 U.S.C. § 156.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571)272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: A. David Joran
Pfizer Inc.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

RE: Chantix™ (varenicline)
FDA Docket No. 2007E-0010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 16 2007

Re: Chantix
Docket No.: 2007E-0010

The Honorable Jon Dudas
Undersecretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Dudas:

This is in regard to the application for patent term extension for U.S. Patent No. 6,410,550, filed by Pfizer, Inc., under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the application and have determined the regulatory review period for Chantix (varenicline tartrate), the human drug product claimed by the patent.

The total length of the regulatory review period for Chantix (varenicline tartrate) is 2,401 days. Of this time, 2,219 days occurred during the testing phase and 182 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: October 15, 1999.

   The applicant claims September 15, 1999, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was October 15, 1999, which was thirty days after FDA receipt of the IND.

2. The date the application was initially submitted with respect to the human drug product under section 505 of the Federal Food, Drug, and Cosmetic Act: November 10, 2005.

   FDA has verified the applicant's claim that the new drug application (NDA) for Chantix (varenicline tartrate) (NDA 21-928) was initially submitted on November 10, 2005.

3. The date the application was approved: May 10, 2006.

   FDA has verified the applicant's claim that NDA 21-928 was approved on May 10, 2006.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: A. David Joran
Pfizer Inc.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

subcommittee update to the Science Board on the progress of the review of the agency's science programs. The Science Board will then hear about and discuss the subcommittee review of the NARMS Program including the public meeting regarding the NARMS Program on April 10, 2007, and subsequent deliberations.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. We are extending the written submission deadline based upon the amended **Federal Register** notice. Written submissions may be made to the contact person on or before June 9, 2007. Two oral presentations from the public will be scheduled between approximately 10:45 a.m. and 11:45 p.m., and 3:15 p.m. and 4:15 p.m. Those desiring to make formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before June 9, 2007. Time allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing sessions. The contact person will notify interested persons regarding their request to speak by June 9, 2007.

This notice is issued under the Federal Advisory Committee Act (5 U.S.C. app.2) and 21 CFR part 14, relating to the advisory committees.

Dated: June 1, 2007.

Randall W. Lutter,

Associate Commissioner for Policy and Planning.

[FR Doc. 07–2829 Filed 6–4–07; 11:10 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2007E–0010]

Determination of Regulatory Review Period for Purposes of Patent Extension; CHANTIX

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for CHANTIX and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments.*

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy (HFD–007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the human drug product becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product CHANTIX (varenicline tartrate). CHANTIX is indicated as an aid to smoking cessation treatment. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for CHANTIX (U.S. Patent No. 6,410,550) from Pfizer, Inc., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated January 26, 2007, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of CHANTIX represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for CHANTIX is 2,401 days. Of this time, 2,219 days occurred during the testing phase of the regulatory review period, while 182 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) became effective*: October 15, 1999. The applicant claims September 15, 1999, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was October 15, 1999, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the act*: November 10, 2005. FDA has verified the applicant's claim that the new drug application (NDA) for CHANTIX (NDA 21–928) was initially submitted on November 10, 2005.

3. *The date the application was approved*: May 10, 2006. FDA has verified the applicant's claim that NDA 21–928 was approved on May 10, 2006.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 545 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments and ask for a redetermination by August 6, 2007. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence

during the regulatory review period by December 4, 2007. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Division of Dockets Management. Three copies of any mailed information are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document.

Comments and petitions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: May 2, 2007.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. E7–10915 Filed 6–6–07; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 1998D–1232] (formerly 98D–1232)

Guidance for Industry and Food and Drug Administration Staff; Assayed and Unassayed Quality Control Material; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of the guidance for industry and FDA staff entitled "Assayed and Unassayed Quality Control Material." The guidance describes FDA's current practices concerning assayed an unassayed quality control material, including information to include in a 510(k) for assayed quality control material, as well as labeling recommendations.

DATES: Submit written or electronic comments on this guidance at any time. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the guidance document entitled "Assayed and Unassayed Quality Control Material" to the Division of Small Manufacturers, International, and Consumer Assistance (HFZ–220), Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850. Send one self-addressed adhesive label to assist that office in processing your request, or fax your request to 240–276–3151. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the guidance.

Submit written comments concerning this guidance to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments.* Identify comments with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Carol Benson, Center for Devices and Radiological Health (HFZ–440), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 240–276–0396.

SUPPLEMENTARY INFORMATION:

I. Background

This guidance document provides recommendations to manufacturers regarding preparation of premarket notifications and labeling for quality control (QC) material. These materials are intended to monitor reliability of a test system and help minimize reporting of incorrect test results. They are often the best source of ongoing feedback that a laboratory has to monitor whether results reported to physicians are sufficiently reliable. QC materials may be marketed together with a specific test system, or alternatively, for more general use.

Both assayed and unassayed QC materials are discussed in the guidance document. Both types of QC materials are subject to FDA's Quality System Regulation (part 820 (21 CFR part 820)) and labeling regulation (§ 809.10 (21 CFR 809.10)). However, most types of unassayed QC materials are exempt from premarket notification. (See "Classification and Identification of QC Material" of the guidance document for exceptions.) Although premarket notifications are number required for unassayed QC materials, some aspects of this guidance document concerning labeling, stability, and matrix effects are still relevant for these materials.

The draft version of this guidance was issued February 3, 1999. FDA received one set of comments on the draft guidance document during the comment period. The document reflects FDA's consideration of the comments and has also been updated to provide clarification as needed.

II. Significance of Guidance

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the agency's current thinking on assayed and unassayed quality control material. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

III. Electronic Access

Persons interested in obtaining a copy of the guidance may do so by using the Internet. To receive "Assayed and Unassayed Quality Control Material; Availability," you may either send an e-mail request to *dsmica@fda.hhs.gov* to receive an electronic copy of the document or send a fax request to 240–276–3151 to receive a hard copy. Please use the document number (2231) to identify the guidance you are requesting.

CDRH maintains an entry on the Internet for easy access to information including text, graphics, and files that may be downloaded to a personal computer with Internet access. Updated on a regular basis, the CDRH home page includes device safety alerts, **Federal Register** reprints, information on premarket submissions (including lists of approved applications and manufacturers' addresses), small manufacturer's assistance, information on video conferencing and electronic submissions, Mammography Matters, and other device-oriented information. The CDRH web site may be accessed at *http://www.fda.gov/cdrh.* A search capability for all CDRH guidance documents is available at *http://www.fda.gov/cdrh/guidance.html.* Guidance documents are also available on the Division of Dockets Management Internet site at *http://www.fda.gov/ohrms/dockets.*

IV. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collections of information in 21 CFR part 610 have been approved under OMB control number 0910–0206; the collections of information in 21 CFR part 807 have been approved under OMB control number 0910–0120; the collections of information in § 809.10

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 21 2008

Re: Chantix
Docket No. 2007E-0010

The Honorable Jon Dudas
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Dudas:

This is in regard to the patent term extension application for U.S. Patent No. 6,410,550 filed by Pfizer, Inc., under 35 U.S.C. § 156. The patent claims Chantix (varenicline tartrate), new drug application (NDA) 21-928.

In the June 7, 2007, issue of the Federal Register (72 Fed. Reg. 31588), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before December 4, 2007, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: A. David Joran
Pfizer Inc.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

APR - 8 2008

A. David Joran
PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,410,550

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 6,410,550, which claims the human drug product CHANTIX® (varenicline), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 544 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 544 days.

The period of extension, if calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of June 7, 2007 (72 Fed. Reg. 31588), would be 799 days. Under 35 U.S.C. § 156(c):

Period of Extension	=	½ (Testing Phase) + Approval Phase
	=	½ (2,219 days - 985) + 182 days
	=	799 days (2.2 years)

Since the regulatory review period began October 15, 1999, before the patent issued (June 25, 2002), only that portion of the regulatory review period occurring after the date the patent issued has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). (From October 15, 1999, to and including June 25, 2002, is 985 days; this period is subtracted for the number of days occurring in the testing phase according to the FDA determination of the length of the regulatory review period.) No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

However, the 14 year exception of 35 U.S.C. § 156(c)(3) operates to limit the term of the extension in the present situation because it provides that the period remaining in the term of the patent measured from the date of approval of the approved product plus any patent term extension cannot exceed fourteen years. The period of extension calculated above, 799 days, would extend the patent from November 13, 2018, to January 20, 2021, which is beyond the 14-year limit (the approval date is May 10, 2006, thus the 14 year limit is May 10, 2020). The period of extension is thus limited to May 10, 2020, by operation of 35 U.S.C. § 156(c)(3).

Accordingly, the period of extension is the number of days to extend the term of the patent from its original expiration date, November 13, 2018, to and including May 10, 2020, or 544 days.

The limitations of 35 U.S.C. 156(g)(6) do not operate to further reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	6,410,550
Granted:	June 25, 2002
Original Expiration Date[1]:	November 13, 2018
Applicant:	Jotham Wadsworth Coe, *et al.*
Owner of Record:	Pfizer Inc.
Title:	Aryl Fused Azapolycyclic Compounds
Product Trade Name:	CHANTIX® (varenicline)
Term Extended:	544 days
Expiration Date of Extension:	May 10, 2020

[1]Subject to the provisions of 35 U.S.C. § 41(b).

Any correspondence with respect to this matter should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

By FAX: (571) 273-7728

Telephone inquiries related to this determination should be directed to Raul Tamayo at (571) 272-7728.

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: CHANTIX® (varenicline)
FDA Docket No.: 2007E-0010

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JUN 24 2008

A. David Joran
PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,410,550

Dear Mr. Joran:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 6,410,550 for a period of 544 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Inquiries regarding this communication should be directed to Raul Tamayo by telephone at (571) 272-7728, or by e-mail at raul.tamayo@uspto.gov.

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: CHANTIX® (varenicline)
FDA Docket No.: 2007E-0010

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	6,410,550
(45)	ISSUED	:	June 25, 2002
(75)	INVENTOR	:	Jotham Wadsworth Coe, *et al.*
(73)	PATENT OWNER	:	Pfizer Inc.
(95)	PRODUCT	:	CHANTIX® (varenicline)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 6,410,550 based upon the regulatory review of the product CHANTIX® (varenicline) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 544 days

from November 13, 2018, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the United States Patent and Trademark Office to be affixed this 16th day of June 2008.

Jon W. Dudas
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	1/31/2020	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC., PFIZER PRODUCTS INC., PF PRISM C.V. and C.P. PHARMACEUTICALS INTERNATIONAL C.V.	VIWIT PHARMACEUTICAL CO., LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,410,550 B1	6/25/2002	Pfizer Inc.
2	6,890,927 B2	5/10/2005	Pfizer Inc.
3	7,265,119 B2	9/4/2007	Pfizer Inc.
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
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In the above---entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1---Upon initiation of action, mail this copy to Director Copy 3---Upon termination of action, mail this copy to Director
Copy 2---Upon filing document adding patent(s), mail this copy to Director Copy 4---Case file copy

AO 120 (Rev. 08/10)

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Copy 1---Upon initiation of action, mail this copy to Director **Copy 3---Upon termination of action, mail this copy to Director**
Copy 2---Upon filing document adding patent(s), mail this copy to Director **Copy 4---Case file copy**